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# BULLETIN

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## THE BALTIMORE EPIDEMIC OF STREPTOCOCCUS OR SEPTIC SORE THROAT AND ITS RELATION TO A MILK SUPPLY.

By LOUIS P. HAMBURGER, M. D.,

*Associate in Medicine, The Johns Hopkins University.*

### I.

In the Journal of the American Medical Association of April 13, 1912, there appeared a preliminary report of "An Epidemic of Septic Sore Throat" which prevailed in Baltimore in the preceding February and March. The infection was due to a streptococcus and was conveyed by an infected milk supply.

It is now possible to supplement the preliminary statement with the further confirmatory evidence of a study of 35 households representing 92 cases of the infection. These, together with a number of interesting cases, descriptions of which were communicated to me through the courtesy of many of my colleagues, furnish the basis of the present report.

The recognition of the epidemic followed when during the month of February, 1912, it became apparent to a number of practitioners of Baltimore that there was prevalent in the city an infectious disease of unusual severity of which the most constant sign was an inflammation of the fauces, in other words, a sore throat.

The malady was characterized by a sudden onset, high and irregular fever, inflammation of the fauces of varying degree, marked enlargement of the cervical glands particularly in the case of children, and a course much longer and attended with many more complications than the usual types of tonsillitis.

The results of cultures taken from patients' throats and of the examination of smears from the inflammatory exudates complicating the disease were strikingly uniform. Streptococci were always revealed. Thus, the discharge after para-

centesis of the ear-drum in the case of a child 5 years old, ill of the infection, showed within leukocytes numerous pairs of Gram positive diplococci (Plate I, A), while a culture from the secretion of the opposite ear discovered the cocci in chains still retaining their diplococci arrangement (Plate I, B). In 19 cases the bacteriologic examination was undertaken and each time a streptococcus was obtained, most often in pure culture. In this way it was recovered not only from the fauces and otitic exudate, but from suppurating lymph-nodes, from an abscess beneath the gastrocnemius muscle, from the peritoneum during laparotomy and from the blood of the femoral vein at autopsy.

The organism was studied at first in Dr. Charles Simon's laboratory by Dr. Simon and his associate, Dr. G. Howard White, and later by many other laboratory workers. These investigators have found that in the direct smears the organism often appears as an end to end diplococcus, intracellular in some specimens. Each pair seems surrounded by a halo but in the early specimens no envelope could be stained. Subsequently, however, capsules were repeatedly, though not invariably, demonstrated in smears from the inflammatory exudates. On culture media, however, the capsules are lost but the streptococcus again appears encapsulated when recovered from the blood of a mouse which had been previously inoculated. It is a Gram positive organism.

On agar it grows in dew-like droplets. It coagulates and acidifies milk, and in this liquid it develops in long chains with end to end arrangement and sometimes in tetrad form,



division having taken place in two planes (Plate I). The organisms are not dissolved by bile salts. Blood-agar plates show a hemolytic zone around individual colonies. In broth the cocci cause uniform turbidity. Inulin is not fermented.

A mouse inoculated intravenously with one of the strains died in 72 hours and from its blood an encapsulated streptococcus was recovered.

Heated in milk to a temperature of 145° F. for twenty minutes the organism is killed.

Almost simultaneously with the demonstration of this streptococcus Davis and Rosenow<sup>1</sup> published a description of a peculiar streptococcus obtained in the course of an epidemic of sore throat prevailing in Chicago just before the Baltimore

they may be identical and that any differences which may exist may be caused by environmental factors.

A feature of the Baltimore epidemic which could not fail to attract attention was the large number of cases appearing suddenly within a few weeks in the month of February, 1912. A few cases apparently similar had been observed during the early winter months.

In the latter part of November and in December, 1911, I attended two children who were mildly affected with sore throat, and presented visible cervical glandular enlargements. They remained the only ones infected in the two households in which they lived.

On January 10, 1912, I saw a boy, 2 years old, suffering with tonsillitis. He subsequently developed marked symmetrical cer-

				FEBR	UARY	1912
				1	2	3
4	5	6	7	8	9	10
			.			
11	12	13	14	15	16	17
	.	..	.	.	.	.
18	19	20	21	22	23	24
.		....	.	....	....	....
25	26	27	28	29	MARCH 1912	
	.	...	..	.	..	.
3	4	5	6	7	8	9
10	11	12	13	14	15	16
			.			
17	18	19	20	21	22	23

The date of onset of the first case of "septic sore throat" in each of 35 households during February and the first half of March, 1912. These 35 households represented 92 cases of the infectious disease.

FIG. 1.

outbreak. It is obviously the same organism and the same infectious disease.

In a more recent communication Davis<sup>2</sup> concludes that the relation of this streptococcus of epidemic or septic sore throat to the ordinary streptococcus pyogenes is very close. Like the common hemolytic strain it causes multiple arthritis when injected into rabbits in very small doses. Occasionally, endocarditis results. In larger doses it kills guinea pigs and rabbits in from 24 to 48 hours. He ventures the opinion that

<sup>1</sup> Davis and Rosenow: An Epidemic of Sore Throat Due to a Peculiar Streptococcus. J. Am. M. Assn., March 16, 1912, 773.

<sup>2</sup> Davis, David J.: Bacteriologic Study of Streptococci in Milk in Relation to Epidemic Sore Throat. J. Am. M. Assn., June 15, 1912, 1852.

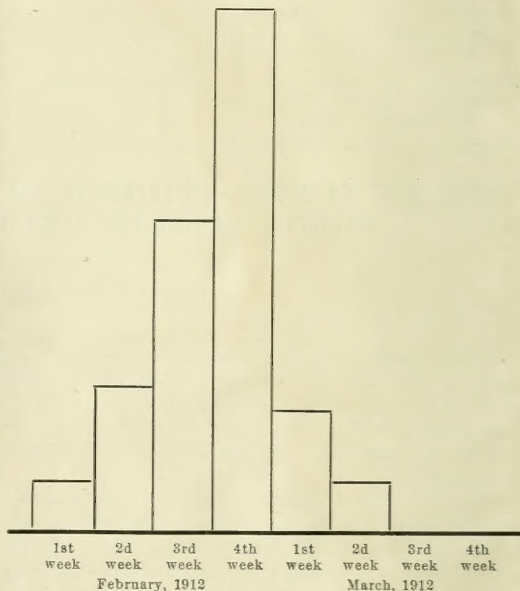


Chart showing the number of initial cases of "septic sore throat" in 35 households in February and first half of March, 1912, according to the weeks in which they occurred.

FIG. 2.

vical buboes and otitis media. The duration of his illness was 12 weeks. In quick succession his mother, an aunt and a maid were attacked by a severe sore throat. All three of these early affected households derived milk from the dairy which later came under suspicion.

In February, however, the cases multiplied, as the accompanying diagrams illustrate.

In Fig. 1 the squares represent the days of February and March, 1912. Each dot represents a household and is placed in the square corresponding to the day on which the first case of septic sore throat appeared in that family. It will be seen that the dots accumulate in the third and fourth weeks of February and then quickly disperse.

Fig. 2 represents a classification of the first cases in each of these households according to the weeks of February and March,



1912, in which they appeared. The column in the first week of February represents one household, the column in the second week four households, the column of the third week has risen to 10, while in the fourth week 16 households present the infection for the first time. Then the diminution in height of the column shows that by the middle of March newly infected households were not seen in my practice.

Throughout the latter half of March and the month of April there were many sore throats and in cultures made from these, streptococci were obtained, but clinically, with only one exception known to me, these cases were not accompanied by the septic complications which characterized the sore throat

Dairy M	Dairy XYZ
.	. . . . .
	. . . . .
	. . . . .
	. . . . .
	.
Dairy N	Dairy O
.	
Dairy P	Miscellaneous Dairies

The milk supply of thirty-five (35) households in which "septic sore throat" appeared in February and the first half of March, 1912. The five dairies shown above are the largest in Baltimore.

Fig. 3.

now under discussion. Moreover, while the septic sore throats of February and the first half of March clearly exhibited a relation to the milk supply, these later and milder sore throats showed no traces of the milk route. They occurred in prosodemic fashion: namely, they appeared to be transmitted from individual to individual through various channels of communication.

The assumption that the infection might have been conducted through one of the general carriers of epidemic disease, such as milk, was ventured because of the explosive character of the outbreak, as illustrated by the foregoing diagrams, because of the wide distribution of the cases throughout the

city and in view of the Boston outbreak to which reference will subsequently be made.

Accordingly there was instituted an inquiry regarding the milk supply of the 35 households in which the type of sore throat under discussion prevailed, with the noteworthy result graphically depicted in Fig. 3. It will be seen that 33 of the 35 infected households derived their milk from one and the same dairy, which is designated XYZ.

However striking this coincidence of dairy and disease may be, it is obvious that no valid conclusion can be drawn unless a comparison is made with the percentage of households in the city supplied by each of the various dairies. Such an inquiry could not be completed. It may be said, however, that the 35 households are distributed through the northern and western sections

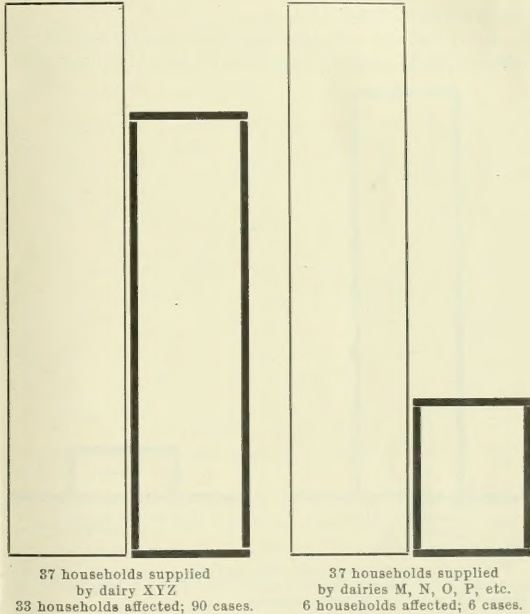


Chart comparing two groups of households: the first, supplied by the XYZ dairy and the second, chiefly by dairies M, N, O, and P.

The heavy column represents the number of households in which "sore throat" appeared in February and the first half of March, 1912.

Fig. 4.

of Baltimore and those sections are supplied chiefly by the five dairies indicated in the diagrams. It is said that dairy M makes the greatest number of deliveries. The conclusion that the streptococcus infection travelled along the route of dairy XYZ is much strengthened by the succeeding diagrams.

In Fig. 4 a comparison is drawn between two groups of 37 households each; the first supplied by dairy XYZ and the second principally by dairies M, N, O and P, the five being the largest dairies in the city.

The second group was selected in alphabetic order from a list of households on which I am in attendance, the only other basis of selection being that each of them should contain one or more children.

The heavy columns represent the number of households in which sore throat of any variety appeared in February and the first half of March, 1912. In the first group, supplied by dairy XYZ 33 households were affected with a total of 90 cases. In the second group of 37 households, chiefly supplied by dairies M, N, O and P, six households were affected, one case in each house.

The next diagram (Fig. 5) offers even more conclusive evidence. Here are represented the percentages of individuals suffering from sore throat during the period under consideration in two "homes" in the same section of the city, and occupied by trained nurses. The one was supplied by dairy XYZ and the percentage of nurses suffering from sore throat in this home rose to 71.4 per cent contrasting with 8.3 per cent in the home supplied by dairy O.

Additional and more gruesome evidence is furnished by the chart (Fig. 6) which represents the relation of 16 deaths from

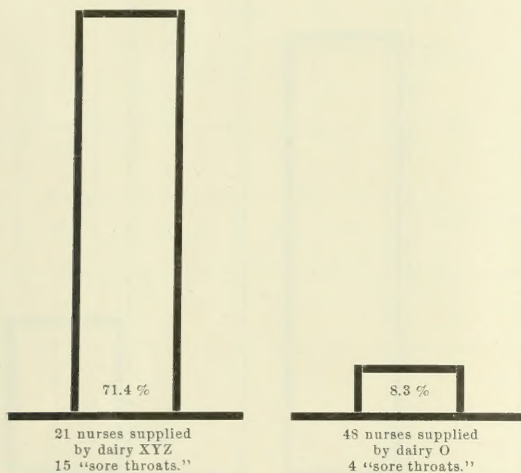


FIG. 5.

The percentage of individuals suffering from "sore throat" in February and the first half of March, 1912, in two "homes" supplied by two dairies and occupied by trained nurses.

septic sore throat to the milk supply of the households in which they occurred. Fourteen are charged against dairy XYZ, while in the case of two the milk supply was unknown.

The first of these two is represented by Dr. Mayo's patient who died of streptococcus peritonitis at the Hospital for the Women of Maryland before the milk conduction was suspected. The second is an adult whom I saw with Dr. Finney, and who died two days later of peritonitis. She was too ill to interrogate at the time. In the XYZ square four crosses represent Dr. Rührh's patients. One each is furnished by Drs. Pollis, Knox, Pancost, Pennington, Shipley, Urquhart, and three are contributed by me.

For statistical purposes it would have been more satisfactory to have had a larger number of observations as a basis for the inquiry. With this object in view the United States Public Health Service offered its assistance, and accordingly Dr. Wade H. Frost was assigned to Baltimore, and on April 26,

1912, assumed charge of the work with the cooperation of the Baltimore Health Department. The epidemic was at an end when this investigation began, so that he experienced difficulty in selecting cases from the records of physicians at such a late date. Nevertheless, Dr. Frost was able to communicate to me the following note:

"I was to some extent disappointed, not being able to collect as extensive records as I had hoped to get. I gathered only about 600 cases, probably not more than a fourth of the total cases, very likely much less than a fourth . . . I have records of 31 deaths of which 26 were almost certainly, and the others quite

Dairy M	Dairy XYZ
	† † † †
	† † † †
	† † † †
	† †
Dairy N	Dairy O
Dairy P	Unknown Milk Supply
	† †

11 children. 5 adults.

The relation of sixteen deaths from "septic sore throat" to the milk supply of the households in which they occurred.

The five dairies shown above are the largest in Baltimore.

FIG. 6.

probably due to this infection. My figures so far as I have analyzed them bear out your conclusions."<sup>3</sup>

<sup>3</sup> As this paper is submitted for publication Dr. Frost's elaborate epidemiologic study appears in The Public Health Report of November 22, 1912 (Vol. XXVII, No. 47). It is followed by a bacteriologic study of the outbreak by William Royal Stokes, M. D., and F. W. Hachtel, M. D. In their summary, attention is called to the inefficiency of the "flash" method of pasteurization which had been employed in the dairy up to the time of the epidemic. They venture the opinion that it is "reasonably" certain that the infection was caused by the streptococci of mastitis, cases of which were discovered in the herds supplying this dairy. No history of the presence of sore throats on the farms could be elicited.



Another link in the chain of circumstantial evidence that the streptococcus infection under discussion coincided with a milk supply was furnished by the proprietor of the dairy in question. Until this mishap the dairy employed the unreliable "flash" method of pasteurization. Following the recognition of the fact that the overwhelming number of primary cases developed along the route of his deliveries, the proprietor of the suspected dairy volunteered the information that during the rigorous winter weather of the latter part of January it was necessary to make repairs in the room in which the pasteurizer was situated, and for the time it was disabled. Certain it is that the milk was not heated during a period beginning January 28, 1912, and unpasteurized milk was delivered from that date through an undetermined part of February. It was thought that during such extreme cold the risk of incubating a pathogenic organism was practically negligible. It is, therefore, fair to assume that the organism was conveyed in raw or inadequately heated milk during the latter part of January and for some time in February, 1912. It was not until March 15 that, through the medium of the press, the public was advised to boil milk. During the ensuing week the proprietor of the incriminated dairy promptly changed its method of "pasteurization" from the "flash" system to the holding device.

The ultimate source of the infection was not discovered. The dairy derives its supply from numerous Maryland farms, but it is said that there was no evidence of an epidemic of either human or bovine disease on the premises of its tributaries.

In contrast with similar epidemics of streptococcus or septic sore throat in eastern Massachusetts<sup>4</sup> and Norway<sup>5</sup> where adults were chiefly affected, children were as frequently and more severely attacked in the Baltimore outbreak. Of the 92 patients 45 ranged in age from 4 months to 15 years, while 47 were between 16 and 65 years old. The oldest sufferer of whom I have knowledge, but who is not included in this list is a lady of 82 years. There were 61 females and 31 males in the series.

That children were most seriously ill is shown by the age distribution of the 16 deaths depicted in Fig. 7. Of these, 11 were children and 5 were adults.

The incubation period was short, probably three days.

A nurse who came into one of these households on Wednesday, February 21, and who until then had not partaken of the milk of dairy XYZ, developed the sore throat Friday night, February 23.

The onset of the malady was sudden and was usually characterized by a chill or chilly sensations. The head, back and limbs ached. In an infant 23 months old the illness was initiated by a convulsion.

There was pain on swallowing. The appearance of the throat varied. Every type of faucial inflammation was represented. Perhaps the most frequent lesion was a dusky red

discoloration of the fauces, a faucitis. In other cases there was a typical follicular tonsillitis, and in some, a membranous exudate resembling the lesion of diphtheria. Again, there was much peritonsillar infiltration which in some adults led to the formation of an abscess, to the development of a "quinsy" requiring surgical intervention. Absence of the tonsils did not preclude the development of the infection. In most of the severe examples of the malady the faucial lesion was of small import as compared with the constitutional disturbances.

The temperature rose rapidly; in one case, to 106.6° F. The curve was very irregular. The duration of the fever was largely dependent on the septic complications. At times, however, the fever continued after the faucial lesion had subsided and no other foci of inflammation could be detected to account for it. With the onset of suppurative processes the temperature assumed the usual intermittent type. Fig. 8 is a copy of the temperature chart illustrating the four weeks illness of a child 23 months old.

Peritonitis	"Sepsis"
† † †	† † † †
† † †	
† † †	
Erysipelas	Undetermined
†	† †

11 children. 5 adults.

The classification of sixteen deaths from "septic sore throat" according to the terminal event.

FIG. 7.

**Convulsion at onset; follicular tonsillitis; cervical bubo; rhinitis; œdema of eyelids; double otitis media; cutaneous abscesses; recovery after a month's illness.**

Irma K., aged 23 months, was suddenly taken ill on the night of February 29, 1912, with vomiting and fever.

On February 26 her mother suffered from a sore throat which confined to her bed for two days.

On March 1 about 6 p. m. she was seized with a convulsion. At half past six she lay in stupor with eyes rolled up and diverging to the right; temperature, 104.4° F., pulse 180. The throat appeared red, the tonsils were swollen, and a follicular exudate was present.

On March 3 (4th day) although the temperature rose to 106.4° F. the follicular deposit had disappeared; there remained only a dusky red discoloration of the fauces. A streptococcus had been cultivated from the throat.

The following day (5th day) a glandular mass was visible beneath the left angle of the jaw.

On March 6 (7th day) the nasal respiration seemed much obstructed and there was a muco-purulent discharge from the nostrils. The lids of the left eye were edematous. At times the child appeared very stuporous but at intervals she was bright, even though the temperature remained high.

<sup>4</sup> Winslow, C. E. A.: Boston M. & S. J., December 14, 1911, 899; J. Infect. Dis., January, 1912, 73-112.

<sup>5</sup> Milk Epidemic in Christiania. Lancet, 1908, I, 107.



March 9, 1912 (10th day): "The child is pale and lies in stupor. The fauces are clear. The cervical bubo is still visible. The ear-drums are normal; the light reflex is apparent. Oedema of the eyelids has disappeared. Lungs are clear on percussion and auscultation. A systolic murmur is audible over all the cardiac valve areas. The temperature has ranged to-day from 101° F. to 103.8° F."

March 13 (14th day): "The cervical glandular mass has diminished in size, so that it is no longer visible. Nevertheless, the temperature rose to 103.1° F."

On March 17 there developed a left otitis media with spontaneous rupture, while six days later the right middle ear became involved.

The temperature remained normal on March 26, and the child began a rapid convalescence complicated, however, on March 31 by the appearance of a number of small superficial abscesses on the legs. She was able to leave the house after a month's illness.

On March 8 the father suffered from a sore throat and was confined to bed for three days.

The household was supplied by dairy XYZ.

Within the first week, usually in the case of children, the deep cervical lymphatic glands in the vicinity of the angle

glandular mass was visible beneath the right angle of the jaw. A week later the adenitis subsided, and although the boy looked pale he was able to leave the bed.

On April 3, 1912, about three weeks after the onset, he vomited, fever returned and he passed eight loose movements during the day, some of which were composed entirely of thick blood-stained mucus. The diarrhoea lasted three days.

At the end of the following week (4th) the cervical bubo which had long since subsided, returned. Eventually, fluctuation was present over the glandular mass and the temperature was intermittent. The abscess was incised on April 25, 1912, and from the evacuated pus a pure culture of a streptococcus was grown.

Coincident with his illness his sister, aged four years, had been similarly affected and underwent an operation for the relief of the cervical suppuration on April 10. Both children recovered.

The household was supplied by dairy XYZ.

In many children even after apparent recovery the buboes remained visible, a source of anxiety to the parents but of no discomfort to the children. It was apparent, too, that in the case of children who were markedly ill the size of the cervical bubo was of prognostic value. A large and persistent bubo

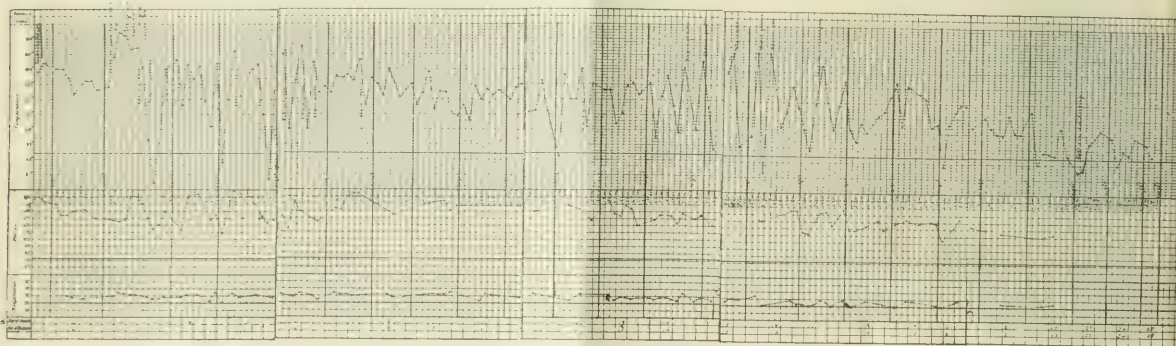


Fig. 8.—Septic Sore Throat.

Temperature chart illustrating the illness of Irma K. (see text).

of the jaw enlarged so as to form visible tumors, often of considerable size and very tender. These buboes gave a characteristic picture to the disorder.

When bilaterally prominent the little ones looked like victims of Hodgkin's disease! The accompanying sketch (Plate I) depicts such an appearance. It is known that because of these swellings the condition was mistaken in several instances for mumps. The fate of the glandular masses was, in the majority, resolution. Even when of large proportion the bubo slowly subsided without the formation of pus. In six cases, however, suppuration occurred. Five of the patients were children and all recovered. The variable course of the adenitis is illustrated by the following case:

**Fancitis; cervical bubo; relapse; diarrhoea; suppurative cervical adenitis; operation; recovery after six weeks' illness.**

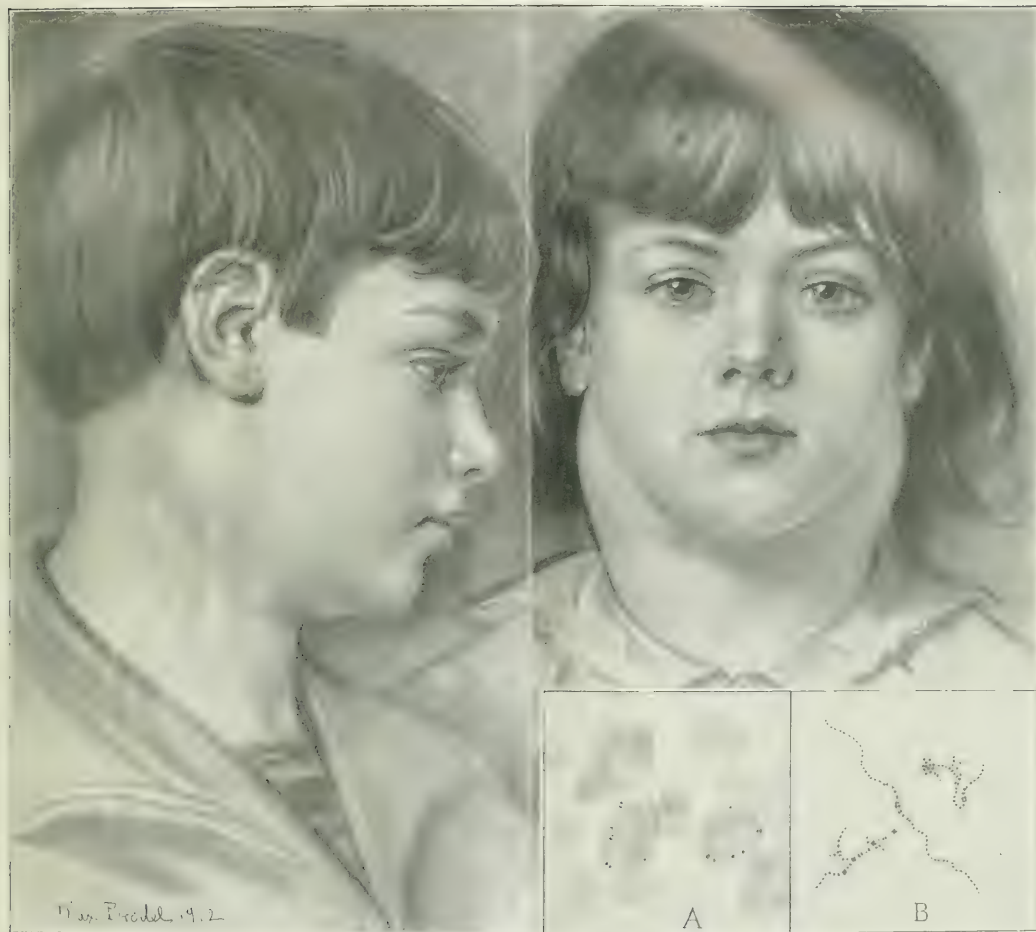
Irving S., aged 9 years, had been feeling ill several days previous to March 13, 1912, when he was seen suffering from fever and sore throat. The fauces were red; temperature 101° F. A

was regarded as of good omen; for, in the fatal cases the glands were only moderately enlarged and quickly diminished in size.

There was no general glandular enlargement. The spleen and edge of the liver were frequently palpable beneath the costal margin. There was a leukocytosis but the differential count gave no noteworthy information.

Prostration was generally marked and the children became pale and thin and gave all the indications of having undergone a severe illness. Nevertheless, the course of the disorder was marked by great variation. In the same household there were those who were so mildly ill that they did not take to bed, while others exhibited all the signs of a profound septicemia for three or four weeks. Even in an individual case there was great irregularity. One day the patient seemed bright and convalescent; on the next, there might be a return of fever, somnolence, and increase in the size of the bubo.

The complications and sequelæ were very numerous. Vomiting at the onset was common. Abdominal pain without sub-



CHILDREN EXHIBITING THE CERVICAL ADENITIS OF SEPTIC SORE THROAT.





sequent development of general peritonitis was a disquieting symptom.

There are notes of two children who cried out with pain in the abdomen. One of them, a girl five years of age, presented abdominal tenderness, which together with muscular rigidity was most marked over the right iliac fossa. The day after the appearance of these symptoms and signs she developed an otitis media and the abdominal pain disappeared.

Enteritis was encountered several times. Glossitis and ulcerative stomatitis were complications in the fatal case, the report of which was communicated to me by Dr. Wells.

**Follicular tonsillitis; cervical adenitis; ulcerative stomatitis; glossitis; death on the 10th day.**

Virginia T., aged 4 years, complained of sore throat on February 27, 1912. She was seen by Dr. Wells on March 1, when she presented a follicular tonsillitis with enlargement of the cervical glands. Temperature 103.5° F. During the ensuing week the mucous membrane of the right cheek ulcerated, the loss of substance extending beneath the tongue on that side. The tongue swelled so that it almost filled the entire oral cavity. The child could be fed only with greatest difficulty. The temperature ranged from 105° F. to 106° F. Early on the morning of March 7 the little girl vomited and died a few minutes after the attack.

The household was supplied by dairy XYZ.

Dysphagia was a noteworthy symptom in a patient observed by Dr. William T. Watson. The following are his notes:

**Faucitis; supraclavicular bubo; dysphagia.**

"Mrs. S. had an inflammation of the tonsils, soft palate and uvula which ran a shorter course than a majority of the cases. She had slight involvement of the glands and jaw. After a few days the superficial cervical glands above the outer end of each clavicle became very much enlarged, so that the swollen masses could be seen across the room. The skin over each of them became red but no abscess formation occurred. As they were subsiding the patient complained of pain along a line corresponding to the whole length of the esophagus which could be felt any time she swallowed food or liquid. This persisted for a number of days."

It is of interest to note in passing that both glossitis and this peculiar dysphagia were described in the Christiania epidemic.\*

Abscess formation occurred in the peritonsillar tissue, in the ear, in the cervical glands and in the superficial and deep tissues of the legs.

It is noteworthy that herpes was absent. Preble<sup>†</sup> has called attention to this fact in giving the clinical history of the Chicago epidemic.

Rhinopharyngitis was often encountered. During the period covered by the epidemic there was occasionally observed a case of bronchitis with râles chiefly unilateral, accompanied by slight dyspnoea and prolonged fever. Although there is no bacteriologic evidence to substantiate the statement, the opinion is ventured that these cases may have represented examples of bronchitis or bronchopneumonia due to the streptococcus.

\* Loc. cit.

† Preble, Robert Bruce: J. Am. M. Assn., June 22, 1912, 1933.

In rare instances there was severe laryngitis. In regard to this complication Dr. Watson has furnished the following description:

"In two cases the disease of the tonsils and palate had spent its force and the patient was apparently recovering when suddenly there was difficulty in swallowing and the mirror showed extensive laryngeal involvement. In one such case the epiglottis could be seen, by simply depressing the tongue, as a large round gelatinous looking mass. In the other case the epiglottis became a large red mass overhanging the larynx and hiding the glottis."

The slow pulse which Preble<sup>‡</sup> mentions as one of the most striking features of the Chicago cases was an infrequent sign in the Baltimore patients.

A girl, 16 years of age, the patient of Dr. Michael Abrams, suffered from sore throat on March 15, 1912. She developed huge bilateral cervical adenitis which did not suppurate. Although the temperature was 103° F. the pulse was only 62.

One patient in this series exhibited an erythema over the legs in the second week of her illness, and at the same period in the course of the disorder in one of Dr. Watson's patients a similar rash resembling the eruption of scarlet fever, lasting only a few hours, appeared over the body and extremities.

Erysipelas was present in three of the children. It was fatal in the case of an infant four months old. The second child, a boy of 23 months, recovered from the cutaneous inflammation, but subsequently died of peritonitis. The third example of erysipelas is remarkable because of the point of departure of the process.

**Erysipelas of the vulva without history of antecedent sore throat; three cases of sore throat and cervical adenitis in the household; recovery.**

Carolyn F., aged 2 years and 9 months, complained on April 11, 1912, of pain on voiding urine.

On February 17 a maid in the household had suffered from a "very sore throat" and marked swellings about the region of the angle of the jaw. She had thought she was "getting the mumps."

On February 21 a second maid had been similarly affected. These two girls were confined to bed for three weeks.

On February 22 Carolyn's sister, aged 4½ years, was taken ill with sore throat and swollen glands.

There is no history of sore throat in the case of Carolyn although a small gland is palpable beneath the right angle of the jaw.

The fauces appear normal. Temperature, 105° F. The mother calls attention to the condition of the vulva. The left labium is swollen, red and very tender, and it is evident that the dysuria bears a relation to this localized inflammation. There is no vaginal discharge and the urine is clear.

On April 13 the temperature continued high (105° F.); the left labium became similarly affected. Dr. Guy L. Hunner saw the child with me, but neither of us could give a satisfactory interpretation of the state of the vulva.

The following day (April 14) the right labium appeared practically normal. The left was also less swollen and less red but extending from the vulva over the antero-external aspect of the left thigh around to the left buttock there was an area over which the skin was rose red and tender. There was a sharp

‡ Loc. cit.

line of demarcation close to the anus. The child cried with pain on making an attempt to evacuate the bowel. The condition was now entirely clear: the inflammation of the vulva was erysipelas.

On April 23, 1912, the skin was desquamating. The child had recovered.

The household's milk was supplied by dairy XYZ.

There were two cases of nephritis among the 92 patients.

Four of the children showed a unilateral oedema of the eyelids.

Inflammation of the serous membranes was observed and included arthritis, tenosynovitis and peritonitis.

There are notes on seven cases of arthritis, four of which occurred in the present series of 92 patients. It was usually polyarticular and prolonged the illness, in some cases, several weeks. It was not associated with endocarditis and the arthritic exudate was never purulent.

**Tonsillitis with exudate; otitis media; multiple arthritis; recovery after an illness of two months.**

Mrs. M. K., aged 49 years, presented on March 5, 1912, an exudate on both tonsils and moderately enlarged cervical glands. Subsequently she developed otitis media and at the end of two weeks multiple arthritis indistinguishable clinically from the type which is usually described as characteristic of "rheumatic fever." She was confined to bed with this complication for six weeks.

In the same house a son and a maid had suffered from sore throat, the latter part of February. Dairy XYZ furnished the milk of the household.

Peritonitis was the terminal event in the majority of the 16 fatalities, as Fig. 7 illustrates. Of the nine who died of peritonitis six were children and three adults. How quickly disaster followed inflammation of the peritoneum is illustrated by the following history:

**Faucitis; no cervical bubo; diarrhoea; peritonitis; death on the fourth day of illness.**

John H., 3 years old, whose sister was suffering from the same streptococcus septicemia, and who himself had been well the previous day, complained on March 4, 1912, of a sore throat.

At 10 a. m. his temperature was 104.4° F. The anterior pillars of the fauces were of a dusky red color. The tonsils were not enlarged, and there was no exudate. The cervical glands were slightly enlarged. At 7 p. m. the temperature was 106° F. During the following day he was delirious and suffered from diarrhoea, having passed 10 small yellow liquid stools.

A culture taken from the throat disclosed the streptococcus previously described. On the morning of the third day, March 6, he was much improved, bright and crying for cake and permission to leave the bed. The rectal temperature at 10.30 a. m. was 100.4° F. Yet, at noon he vomited and the temperature rose so that at 4.30 p. m. it registered 106° F. He had had three liquid stools during the day. Examination of the ears was negative. At 5.30 p. m. he looked very ill. His pale skin presented a purplish mottling. The pulse was of small volume, the abdomen was tender. He begged for water.

It was given repeatedly in small quantity, but was vomited each hour. The child retained consciousness throughout the night although the radial pulse was not palpable; the abdomen became distended, vomiting continued, and at half past eight on the morning of the fourth day of his illness he was dead.

Laparotomy was performed on three adults suffering from this terminal peritonitis. In one of these cases the exudate was purulent; in the other two, a general fibrinous inflammation was present. A streptococcus was isolated from the peritoneal fluid of all.

At the beginning of the Baltimore outbreak of septic sore throat the disorder was diagnosed indefinitely as "grip," and it was not until several fatalities had followed sore throats that the unusual character of the epidemic infection became evident. Thereafter, the diagnosis was based chiefly on the clinical picture and the course of the malady. Fever persisted longer than in the usual types of sore throat. In many cases the severe constitutional disturbance was out of proportion to the intensity of the faucial lesion.

From the faucial lesion alone the diagnosis could not be made. Bacteriologic examination of the throat, disclosing on smears diplococci and on culture media chains of cocci, was easily and quickly carried out and confirmed the nature of any suspected faucial inflammation.

The fauces appeared to be the portal of entry, but occasionally there arose the question as to the possibility of streptococci gaining access to the body through a channel other than the throat. Carolyn F., who suffered from erysipelas without a sore throat having been detected, is a case in point.

From the foregoing considerations it will be seen that the cases which were clinically designated "septic sore throat" fall into three groups.

The first group is characterized by inflammation of the fauces associated with marked visible enlargement of the cervical glands.

There is a second group with or without the physical signs just mentioned, but presenting some metastatic septic or streptococcal complication, such as erysipelas, arthritis, abscesses or peritonitis.

In the third group are included cases of sore throat occurring in households in which one or both of the first two types prevailed.

It was not possible to establish an accurate prognosis in the individual case. The history of John H. illustrates the unexpected fatal issue. Large and persistent cervical buboes warranted a favorable outlook.

Of the 92 patients three died. Because of my interest in the epidemic Dr. Finney's patient dying of peritonitis came under observation two days before death and can properly be excluded from the estimate of the death rate in this series. The rate of mortality would then be about two per cent.

The treatment of sufferers from "septic sore throat" did not vary from the usual management of febrile patients. No advantage seemed to be derived from direct faucial medication.

Aspirin (acetylsalicylic acid) was used in almost every case and brought temporary relief from the pain in various parts of the body. Hexamethylenamin was frequently administered but without apparent beneficial result. Vaccine therapy was not employed.

Realizing that the cervical buboes, even when of large di-

mensions, usually disappeared spontaneously, surgical intervention was not practised unless fluctuation was distinctly appreciable.

## II.

That milk is a medium of transmission of some infectious diseases to man is no longer doubted. There come to mind at once tuberculosis and typhoid fever and the less familiar milk epidemics of scarlet fever, diphtheria and gastroenteritis. But, it is not generally known that the first clinical record of probable conveyance of disease through milk was that of Sagar, who in 1764 ventured the opinion that a number of throat affections and aphthous ulcers were due to drinking the milk of a certain cow.<sup>9</sup>

Nevertheless, since that early date, records of milk-borne sore throat outbreaks have been comparatively rare. The Baltimore epidemic is the second recorded American outbreak of severe throat infection connected with a milk supply.

The first is the eastern Massachusetts epidemic of May, 1911, described by C. E. A. Winslow.<sup>10</sup> Simultaneous with the publication of the preliminary report of the Baltimore streptococcus infection there appeared a note on the probable spread of a similar epidemic in Chicago through milk.<sup>11</sup>

Similar outbreaks have been more frequently observed in Great Britain, where the affection is often described as "septic sore throat," and it is from English source that this term has been adopted.

Recently 18 English epidemics have been gathered and critically examined by Dr. William G. Savage.<sup>12</sup> They date from the outbreak in March, 1880, among the boys at Rugby School to the large epidemic of April, 1905, at Colchester, carefully studied by Dr. Savage himself.

With the addition of the Norwegian report<sup>13</sup> the recorded milk-borne sore throat outbreaks now number 22. In practically all the symptomatology is the same. Whenever a bacteriologic examination was made a streptococcus was found in cultures from the throat and other foci of inflammation. In nearly all the evidence that the infective agent was spread by milk is fairly satisfying, but in a great number the final source of the infection is by no means clear.

There is a group embracing 10 epidemics in which there is reasonable certainty that the infection was derived from a cow or cows suffering from mastitis or from ulcerated teats.

There is a second class including five outbreaks in which it is possible to assume that the milk was polluted by contact with individuals suffering from sore throat. But in seven the evidence is not satisfactory enough to venture even an hypothesis as to the origin of the infection.

<sup>9</sup> Quoted by Stokes, Wm. Royal and Clement, A. W.: An Epidemic of Purulent Inflammation of the Milk Ducts Affecting Seventy Cows. Maryland M. J., January 9, 1897.

<sup>10</sup> Loc. cit.

<sup>11</sup> Miller, J. L. and Capps, J. A.: Epidemic of Sore Throat due to Milk. J. Am. M. Assn., April 13, 1912, 1111.

<sup>12</sup> Savage, William G.: Milk and the Public Health, 1912, 91.

<sup>13</sup> Loc. cit.

The epidemic at Christiania in the fortnight of March, 1908, embracing 548 reported cases, can probably be admitted to the first division, since it is stated that "it (the outbreak) was speedily traced to the milk supply of one dairy and thence to a cow with a diseased udder. The cow was slaughtered and a bacteriological examination of the abscess found in the udder led to the isolation of streptococci in every way identical with the streptococci obtained from patients suffering from the epidemic."<sup>14</sup>

According to Dr. Savage's critique of the Colchester epidemic of April, 1905, involving at least 600 persons it is "nearly certain" that here, too, the infection was of bovine origin.

The milkman M. (whose dairy was implicated) obtained his milk from 6 farms . . . Only on farm B were human cases of illness or disease amongst the cows met with. Upon this farm a cow was found in the shed, with the others, suffering from mastitis of one quarter, and which had been noticed to be ill since about April 19. The milk of this cow was being added to the milk up to the time of April 27. The cessation of the outbreak corresponds with the exclusion of the milk of this particular cow . . . The first illness on the farm was that of the farmer himself, who suffered from a severe sore throat, which confined him to bed for 3 or 4 days. He never milked the cows, and said he had very little to do with them. The onset of his illness was April 17, a date which coincided with other cases in the town. This, with other facts renders it nearly certain that he was infected from the milk and was not the source of infection of the milk.<sup>15</sup>

On the other hand, as a result of Winslow's study of the eastern Massachusetts epidemic of septic sore throat he concludes that "probability points to the infection of the milk from the human cases" which were known to be abundant on and in the neighborhood of the farm from which the distributing dairy derived its supply.

The study is based on 1043 cases. The epidemic began on May 8, 1911, rose to a maximum on May 14 and practically ceased after May 28. Forty-eight deaths were attributed to the infection. The cases followed the milk supply of a "carefully supervised" dairy to which farms in the towns of Southboro and Marlboro were tributary. The peculiar sore throat under discussion prevailed in prosodemic form in the towns of Hudson, Marlboro and Southboro during April and May, and in the second week in May it appeared in epidemic fashion in Boston, Brookline, Cambridge, Marlboro and Southboro along the route of the dairy above mentioned. No bovine disease was discovered on the farms, and although there was no record of direct contact of a patient with milk it was thought probable that the infection was due to a human carrier. Dr. Theobald Smith examined 4 cultures made from the internal organs in typical septic cases and isolated streptococci, all apparently of the same type.<sup>16</sup>

Another example of possible human origin of a streptococcus infection of milk is afforded by the report of the Guilford epidemic of 1903 based on a study of 98 infected households.

The outbreak dated from the last week in September to the first of November. The proprietor of the incriminated farm suf-

<sup>14</sup> Loc. cit.

<sup>15</sup> Milk and the Public Health, 1912, 93; Public Health, 1905-6, XVIII, 1.

<sup>16</sup> Loc. cit.



ferred from "quins" the middle of September. His illness antedated the outbreak. He assisted at the milking. Four of the 20 cows on the farm suffered from mastitis, and streptococci virulent to mice were isolated from their milk. It was suggested that they were infected by the farmer and that the mastitis supplied a continuous source of the infection which extended six weeks beyond the illness of the farmer himself.<sup>17</sup>

Capps and Miller's<sup>18</sup> able investigation of the epidemic of streptococcus sore throat in Chicago, December, 1911, disclosed similar conditions on a larger scale: namely, mastitis was epidemic among the cows supplying the milk to the suspected dairy (dairy X), and sore throat of the epidemic type was prevalent among the farmers and milkers. Virulent streptococci with similar cultural properties were isolated from the inflamed udder of a cow and from the human faucial lesion.

The epidemic involved probably 10,000 persons in Chicago. Of 622 patients suffering from septic sore throat 87 per cent used the milk of dairy X. Of 19 fatal cases 79 per cent had partaken of this milk. Although tonsillitis was prevalent in the state of Illinois it was only in Batavia that there was an epidemic similar to that of Chicago, but here the X milk was collected from the farms and pasteurized. Batavia was also in part supplied with this milk. Mastitis involving 4.6 per cent of the cows supplying the dairy was epidemic during the winter months and was worst about the Christmas holidays. Sore throat of the epidemic type was also prevalent on the farms and in this locality.

Davis<sup>19</sup> isolated the peculiar streptococcus to which reference has been repeatedly made both from the milk of a cow exhibiting chronic mastitis and from the fauces of a girl on the same farm, who had been ill with sore throat and arthritis.

The dairy employed the "flash" method of pasteurization by which the milk was momentarily raised to 160° F., but large fluctuations of temperature were demonstrated on the pasteurizer's thermal charts. On several days a minimum temperature of 130° F. was recorded. There was a distinct relation between the days on which the pasteurizer was most inefficient and the subsequent days on which great outbreaks of sore throat occurred.<sup>20</sup>

A final conclusion as to whether the bovine mastitis was the primary source of infection or whether the udder disease was secondary to the milkers' sore throat or whether the bovine and human infections were independent could not be reached in a consideration of the Chicago epidemic.

Thus are raised two questions: are the streptococci of bovine mastitis pathogenic to man, and, can streptococci found in instances of human sore throat produce mastitis in cows? Savage<sup>21</sup> has investigated the problem with the following interesting results: Of 36 cases of mastitis in cows 68 per cent were due to streptococci. Eighty per cent of these strepto-

cocci could be classified as a common type designated as *streptococcus mastitidis*. Nevertheless, it is important to note that in several cases "quite different streptococci" were cultivated. In 16 cases of human sore throat the most prevalent type of organism was what has been designated *streptococcus anginosus*, while a second type was identical with *streptococcus pyogenes*. Now, it was found impossible to differentiate the *streptococcus mastitidis* and the *streptococcus anginosus* either morphologically or culturally, even when the various sugar-alcohol tests were used. While the bovine streptococcus was, as a rule, nonpathogenic to rodents, the *streptococcus anginosus* frequently caused death in mice. Still, Savage considers this distinction one of degree rather than of kind. The functional capacity of the streptococci was further investigated in a series of experiments on the teats of goats. Three streptococci from cases of mastitis in cows set up mastitis in the goats in every instance. Seventeen strains from human origin all failed to evoke mastitis in another series of goats. Two streptococci derived from a case of Ludwig's angina and from a case of acute epiphysitis produced some degree of mastitis in these animals.

Although the experiment is far from conclusive, it is of interest to add that without ill effect Savage infected his own throat with massive doses of the *streptococcus mastitidis* freshly isolated from the mastitis of cows.

Furthermore, he calls attention to the fact that while bovine mastitis is common, sore throat due to milk is rare. Therefore, Savage concludes that the organisms causing the great majority of cases of bovine mastitis are not virulent to man, but that in certain uncommon cases inflammation of the udders of cows may be provoked by streptococci pathogenic to human individuals.

After all is said, the problem of the differentiation of streptococci remains unsolved. It would be of greatest value if there were discovered some convenient method of determining the source and functional characters of these organisms. Certain practical conclusions, however, remain unaffected. Cows suffering from mastitis must be excluded from a milk supply and human individuals suffering from sore throat must be prohibited from handling the milk at any stage from production to delivery. Since these measures can be carried out only in theory, effective pasteurization of a city's milk supply is the only satisfactory method of averting the possibility of such an outbreak of septic sore throat as occurred in Baltimore during the winter of 1912.

### III.

The lessons which can be deduced from the foregoing discussion are embodied in the following conclusions:

1. The undue prevalence of sore throat and other influenzoid affections should be reported to the Municipal Health Department for investigation as to the possibility of milk conduction of the infection.
2. A streptococcus infection when it is introduced into a community through milk possesses an extreme virulence and

<sup>17</sup> Brit. M. J., 1903, II, 1492.

<sup>18</sup> Capps, Joseph A., and Miller, Joseph L.: Chicago Epidemic of Streptococcus Sore Throat and Its Relation to the Milk Supply. J. Am. M. Assn., June 15, 1912, 1848.

<sup>19</sup> Davis, David J.: Bacteriologic Study of Streptococci in Milk in Relation to Epidemic Sore Throat. J. Am. M. Assn., June 15, 1912, 1852.

<sup>20</sup> Capps, Joseph A.: The Role of Milk in the Causation of the Chicago Epidemic of Sore Throat. J. Am. M. Assn., November 9, 1912, 1715.

<sup>21</sup> Milk and the Public Health, 1912, 107-111.

may produce a clinical picture characteristic in some aspects and complicated in many.

3. It is possible that raw milk from any dairy though carefully produced and handled may at some time convey a streptococcus infection.

The dairy, along the route of which the overwhelming number of cases of septic sore throats developed in the eastern Massachusetts epidemic, feeling secure in the elaborate precautions exercised to produce clean milk, did not employ pasteurization. For 28 years this dairy had been furnishing its product to Boston, without mishap, when in May, 1911, the outbreak occurred.

4. From a study of the American epidemics of streptococcus or septic sore throat the importance of thorough pasteurization of clean milk in its final containers under efficient official inspection is clear.<sup>2</sup>

<sup>2</sup> Jordan, Edwin O.: The Case for Pasteurization. J. Am. M. Assn., October 19, 1912, 1450.

In the course of the Chicago epidemic the 70 occupants of the children's wards at the Michael Reese Hospital escaped without developing a single case of sore throat. Fifty-three per cent of the nurses of this hospital were attacked. Both the children's ward and the nurses' home were supplied by dairy X. There was this important difference: the nurses drank the milk "pasteurized" by the dairy's "flash" method, while the milk delivered to the children was pasteurized effectively by the holding system in the hospital itself.

5. If by accident the pasteurizing plant of a dairy is disabled the dairy should notify its patrons to boil the milk.

6. When the price of pasteurized milk is prohibitive it is suggested that the practice of boiling milk should be advocated or instruction in home pasteurizing<sup>3</sup> should be given in medical dispensaries, by visiting nurses and by physicians.

7. Finally, it is obvious that milk inspection as at present conducted is inadequate.

<sup>3</sup> Circular 197, Bureau of Animal Industry, U. S. Dept. Agric., Washington, D. C., April 19, 1912.

## THE EFFECT OF HYPERSENSITIVENESS TO A TUBERCULO-PROTEIN UPON SUBSEQUENT INFECTION WITH BACILLUS TUBERCULOSIS.

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Tuberculosis is a disease of man and of cattle, widespread and devastating. Practical interest, therefore, attaches to the question whether it is possible to obtain a usable protective inoculation against it. Such a practical vaccination for man has not been found, but since the work of Von Behring demonstrated the possibility of artificial immunization in cattle with bovo vaccine, many inoculation preparations have been made and various modes of administering them have been devised.

Römer,<sup>1</sup> in a series of monographs, has published the effects of a primary tuberculosis in animals upon the course of a second infection with tubercle bacilli. Guinea-pigs, sheep and cattle already suffering with inoculation tuberculosis, were reinfected by the cutaneous or by the intracutaneous route, and carefully studied along with control animals. He found that the primary infection was protective, conferring "complete immunity to small reinfesting doses, diminishing the infectiousness of reinfesting doses of moderate size, and leading to a lack of immunity when moderately large doses were injected." Further "to massive amounts of tubercle bacilli, an already tuberculous host is more sensitive than is a normal animal succumbing with the symptoms of acute hypersensitiveness." The one biological reaction constantly present in the animals used in the reinfesting experiments was hypersensitiveness, —hypersensitiveness not only to tuberculin, but to the tubercle bacillus itself. In this condition Römer believes the possible, even the probable, immunization mechanism exists. It is of great interest that he differentiated between hypersensitiveness to the tubercle bacillus (*Tuberkelbacillen-Überempfindlichkeit*); and hypersensitiveness to tuberculin (*Tuberkulin-Überempfindlichkeit*); a differentiation independently recog-

nized by Calmette.<sup>2</sup> This difference between hypersensitiveness to living tubercle bacilli and to tuberculin, both authors consider a fundamental difference and not merely a quantitative one.

Sata,<sup>3</sup> on the basis of immunization experiments made on horses, cattle, guinea-pigs and rabbits, with living and with dead bacilli, as well as with extracts of pulverized organisms, claims to have demonstrated a certain connection between "the hypersensitiveness which developed, and the production of antibodies." "Where hypersensitiveness develops," says Sata, "there immunity appears; therefore it is justifiable to conclude that immunity has developed wherever allergy exists, and since hypersensitiveness may be produced by the toxins of the bacilli, as well as by the bacilli themselves, immunity may be stimulated by the injection of these toxins." Sata did not prove a causal relationship between the hypersensitive state and the immunity, and so far as his experiments are concerned, the opinion may still be entertained that the two conditions are coexistent, without having necessarily a causal interdependence.

Little work has been published to demonstrate the relation of allergy alone to immunity.

Rosenau and Anderson<sup>4</sup> sensitized guinea-pigs with extracts of *B. typhosus* and of *B. coli* and found, in each instance, that the animals so treated were immune to amounts of the respective organisms, fatal to normal guinea-pigs.

In 1907 Vaughan and Wheeler<sup>5</sup> injected guinea-pigs with from 15 to 200 mgm. of tuberculo-protein ("cellular substance," "cell residue," etc.) and one month later inoculated the same animals "with a loop of an avirulent culture of bacillus tuberculosis." They observed that the intraperitoneal



injection of the protein had sensitized the animals so that "the bacilli of the second dose were broken up so rapidly and their poisonous constituents set free so speedily that the animals died." In other words Vaughan and Wheeler demonstrated that as a result of hypersensitiveness to tuberculo-protein, hypersensitiveness to tubercle bacilli had developed.

Duval and Couret,<sup>6</sup> in attempting to produce experimentally the lesions of leprosy in the monkey, failed to do so, until they had sensitized their animals with "large numbers" of leprosy bacilli, "injected at given intervals for a period of months." They stated "that infection is more likely to follow where sensitization is first established, is definitely proved by the specific experiments that we have carried out in a number of laboratory animals. The first injection we assume sensitizes the animal and it may consist of either killed or viable lepra bacilli." Again, "in our experience it has been extremely difficult to produce in the lower animals more than a transient localized lesion with human leprosy material, rich in the specific bacilli, unless the animal is first sensitized, when lesions histologically identical with those produced by pure cultures are easily induced." These observations, so far as we have been able to learn, are the first that would indicate definitely that sensitization with a specific protein can diminish the resistance of an animal to infection with the organism from which the protein was derived.

Krause,<sup>7</sup> in 1911, published the results of a small series of inoculations of living tubercle bacilli into sensitized and into refractory guinea-pigs. The animals, after sensitization with a tuberculo-protein, made according to the method of Baldwin, were each given a subcutaneous injection of 0.1 ccm. of an emulsion of tubercle bacilli, which contained an average of one bacillus to every one or two fields. Sixty-two days after inoculation, the infected animals were killed by a blow on the head. Krause, interpreting his results on the basis of macroscopic tuberculosis, concludes that the refractory animals suffered most "showing the disease pretty well disseminated, and far more tuberculosis than any of the animals that had not been intoxicated, and than any of the controls." The animals that had been sensitized all developed tuberculosis and "as a general thing, the more protein the animal received during preliminary treatment, the less was the resultant infection." In summary he concludes: "Sensitization of non-tuberculous guinea-pigs with tuberculo-protein does not alter their resistance to experimental tuberculous infection. Sensitization to tuberculo-protein and relative immunity (increased resistance) to infection can occur coincidentally in the same animal. Resistance to infection is markedly lowered during the period that a sensitized animal is suffering from symptoms of anaphylactic shock."

In order to test the validity of the assertions of Römer and of Sata, that the hypersensitive state was responsible for the immunity that developed in their animals, the course of infection in animals in which sensitization had been produced apart from infection was noted. This seemed worth while, since if sensitization with non-toxic products led to immunity to infection with living tubercle bacilli, an innocuous prophylactic vaccination might be developed for use in man.

#### THE INFLUENCE OF HYPERSENSITIVENESS TO A TUBERCULO-PROTEIN UPON INFECTION WITH TUBERCLE BACILLI.

The work of Römer (*l. c.*) showed that a primary infection with living tubercle bacilli confers an immunity to reinfection with the organism. Inasmuch as Römer found that hypersensitiveness was the one biological reaction constantly present, he inclined to the view that this condition of altered response might be the protective mechanism which made the animals immune to a second infection. In spite of the apparent proof that the hypersensitive state was the protective factor, certain other possibilities were at once evident. The mere fact that the known antibodies tested for were present only inconstantly, whereas hypersensitiveness was always demonstrable, did not necessarily show that the latter was the true immunizing influence. It is conceivable that other antibodies, the methods of demonstrating the presence of which are not yet known, might have been present. The hypersensitiveness might have been coexistent with and still not causally related to the immunity, or it might have been a baneful factor, in a measure diminishing resistance to infection.

During the four months preceding our interest in this problem, we had been working with a tuberculo-protein and studying the hypersensitiveness developing in guinea-pigs and in rabbits treated with it. It occurred to us, therefore, that the interrelation of hypersensitiveness to this protein and infection with tubercle bacilli, might readily be determined, inasmuch as in animals so treated, antibodies other than sensibilisin would be lacking or present only in minimal quantities.

The tuberculo-protein used for sensitization in the following experiments was made according to a modification of the technique recommended by Baldwin.<sup>8</sup> Three strains of human type tubercle bacilli, H39, received through the courtesy of Dr. A. K. Krause, of the Saranac Laboratory, and H<sub>a</sub> and H<sub>β</sub>, isolated from the sputa of two patients ill with tuberculosis, were inoculated into a number of flasks containing 5% glycerine broth. At the end of several weeks the broth was removed, the bacilli washed several times with 0.85% salt solution, then dried in vacuo and thoroughly ground in a mortar. The pulverized mass was then suspended in water in the proportion of 1 gm. of bacillary powder in each 15 ccm. of distilled water, and extracted for 48 hours at 55° to 60° C. The suspension was filtered through a Berkefeld bougie, and the protein, precipitated from the amber colored fluid with ten volumes of absolute alcohol, was dried in vacuo. The powder so obtained is readily soluble in water and, as the result of numerous experiments, it was found that 10 to 15 mgm. of the material inoculated into the peritoneal cavity of a full grown guinea-pig, is required constantly to produce active sensitization.

It is of some importance to note that the protein thus obtained varied considerably in its sensitizing power, in spite of the fact that great care was taken to employ the same technic in the making of each supply of the preparation. This protein, too, is practically non-toxic, an intraperitoneal injection of as much as 200 mgm. in single or in divided doses failing to cause symptoms when injected into the peritoneal cavity of guinea-pigs of 300 gm. weight.

For inoculation, suspensions of cultures of *Ha* were made as follows:

The organisms grown in 5% glycerin broth were rubbed on the wall of an Erlenmeyer flask, a small amount of sterile salt solution was added, and after the addition of sterile glass beads, the flask was thoroughly shaken for three hours. The fluid was then filtered through cotton to remove clumps, centrifuged and standardized in terms of bacilli in an average field of the oil immersion lens.

In the experiments on rabbits a different method of standardization was used. A small bit of growth on the surface of a glycerine bouillon culture was removed with a platinum tip, dried over calcium chloride and a determined weight of the organism carefully emulsified in a measured amount of 0.8% salt solution.

The amounts of these suspensions used for inoculation varied, as will be noted in the individual protocols.

#### SERIES I.

September 29, 1911. Ten guinea-pigs (1-10) varying in weight from 290 to 330 gm., were each sensitized by the intraperitoneal injection of 15 mgm. of tuberculo-protein dissolved in 1 ccm. of water. After 25 days, one of the animals (1) was tested for anaphylaxis and succumbed in acute shock within 4 minutes. None of the other treated animals were reinjected, inasmuch as experience had shown that this amount of protein almost invariably caused sensitization.

October 23, 1911. The other nine guinea-pigs, 2 to 10, together with nine non-sensitized normal guinea-pigs, 201 to 211, of the same weight, each received in the subcutaneous tissue of the left groin 0.2 ccm. of a suspension of *Ha*, which contained three bacilli in an average field of the oil immersion lens.

December 7. Guinea-pig 7, dead in cage. Weight 200 gm., loss of weight, 75 gm. The lymph glands in the left groin are small and show central plugs of caseation, but there is no local reaction in the subcutaneous tissue about them. The lungs are hyperæmic, and scattered through the parenchyma are many small gray tubercles. The spleen is swollen and studded with many tubercles, none of which are caseous. The other viscera show no tuberculous involvement.

December 11. Guinea-pig 2, found dead in cage. Weight 180 gm., loss of weight 65 gm. There is a large caseous abscess in the left groin, and the regional lymph nodes are swollen and caseating. The lungs are edematous and mottled with gray tubercles, 0.5 to 1.5 mm. in diameter. The spleen is enlarged and shows subcapsular tubercles. The other viscera are apparently uninvolved.

Guinea-pigs 3, 6 and 8, and controls 201, 204, 206 and 208, died on December 14 of an acute intercurrent infection. In all of these the lungs and the spleen showed the presence of tuberculosis and there was also an abscess in each at the site of inoculation. The other animals in this series were immediately killed and the cages cleaned and fumigated.

December 7. Guinea-pig 202, control animal, was etherized and the progress of the disease compared with that in guinea-pig 7. Weight 260 gm., loss of weight 20 gm. There is a small local abscess in the left groin. The spleen is enlarged and studded with gray tubercles. The other viscera are apparently normal.

December 11. Guinea-pig 209 etherized and the lesions compared with those found in sensitized guinea-pig 2. Weight 220

gm., loss of weight 15 gm. There is a local abscess in the left groin, with swelling of the regional lymph glands. The spleen is enlarged and shows many gray tubercles. The other viscera are apparently uninvolved.

Only four animals in Series I were really available for study, and for that reason, the same procedure was repeated in Series II.

#### SERIES II.

December 15. Guinea-pigs 12 to 23, inclusive, each received an injection of 15 mgm. of tuberculo-protein by the intraperitoneal route. Each of these animals was paired with a non-sensitized control animal (guinea-pigs 211 to 240) and on January 9 each received, in the subcutaneous tissues of the left groin, 0.2 ccm. of a suspension of *Ha*, which contained two bacilli in each 24 fields of the oil immersion lens. Ten of the sensitized animals, together with the ten corresponding controls, were killed on the fifty-fifth day after infection and thereafter ten pairs were etherized on the seventieth and on the one hundred and fiftieth day, respectively, for a comparison of the lesions produced.

#### A.

Guinea-pigs 12 to 24, infected twenty-four days after the injection of the tuberculo-protein and guinea-pigs 211 to 221, control, non-sensitized animals, were etherized on March 6, fifty-five days after infection.

Guinea-pig 12. Well nourished, weight 270 gm., gain of weight 10 gm. There is a large caseous abscess in the left groin and the regional lymph glands are enlarged and softened. The spleen is swollen, firm and studded with gray tubercles, 1 to 2 mm. in diameter. The other viscera are uninvolved.

Guinea-pig 13. Emaciated, weight 200 gm., loss of weight 60 gm. There is a small caseous gland in the left inguinal region. The lungs are congested and show a few scattered gray tubercles. The spleen is enlarged, tense and studded with gray tubercles up to 2 mm. in diameter. The other viscera show no gross tuberclosis.

Guinea-pig 14. Emaciated, weight 210 gm., loss of weight 39 gm. The lymph glands in the left groin are necrotic. The lungs are congested and show fairly numerous gray tubercles throughout the parenchyma. The spleen is soft and dotted with numerous gray tubercles. There is no evident disease of the other viscera.

Guinea-pig 15. Well nourished, weight 260 gm. Weight unchanged since infection. The inguinal and the iliac lymph glands on the left side are small and on section show a central plug of caseation. The other viscera, except the spleen, appear normal. The spleen is slightly enlarged, firm, and scattered through it are many tubercles.

Guinea-pig 16. Well nourished, weight 250 gm., gain of weight 10 gm. There is a small caseating abscess in the left groin and the left inguinal lymph glands are swollen and softened. The lungs are pale, emphysematous and show many tubercles. The spleen is riddled with young tubercles.

Guinea-pig 17. Emaciated, weight 200 gm., loss of weight 65 gm. There is a large caseating abscess in the left groin, where the inguinal and the iliac glands are completely replaced by a fibrous sac with yellow caseous contents. The lungs are hyperæmic and show many small tubercles. The spleen contains many miliary tubercles. The other viscera appear normal.

Guinea-pig 18. Well nourished, weight 275 gm., gain of weight 25 gm. Careful examination shows tubercles only in the spleen, where they are numerous, gray in color, and 1 to 1.5 mm. in diameter.

Guinea-pig 19. Well nourished, weight 225 gm., loss of weight 30 gm. There is a fluctuating abscess in the left groin, the contents of which contain many tubercle bacilli. The regional lymph

glands are swollen and softened. The lungs are pale and collapsed and show many tubercles. The spleen is similarly involved. The other organs show no gross lesions.

Guinea-pig 20. Emaciated, weight 190 gm., loss of weight 38 gm. There is a large abscess in the left groin, and the regional lymph glands are swollen and caseating. The spleen is enlarged and mottled with gray tubercles. No other evidence of tuberculosis is found.

Guinea-pig 21. Emaciated, weight 210 gm., loss of weight 50 gm. The lymph glands in the left groin are caseous. The lungs are pink and studded with gray tubercles, 1 to 1.5 mm. in diameter. The spleen is swollen and shows many fresh tubercles. Otherwise the viscera appear normal.

Guinea-pig 22. Under nourished, weight 235 gm., loss of weight 25 gm. There is a large abscess in the left groin. The lungs and the spleen are studded with fresh tubercles; otherwise no evidence of tuberculosis is found.

Guinea-pig 23. Well nourished, weight 245 gm., gain of weight 15 gm. There is a small abscess in the left groin and the lymph glands in the left inguinal and iliac regions are fibrosed. No tubercles are seen in the viscera.

Control, non-sensitized guinea-pigs injected with the same dose of the same suspension on December 15, 1911, and etherized on March 6, 1912.

Guinea-pig 211. Well nourished, weight 290 gm., gain of weight 30 gm. There is no local abscess in the left groin but the deep inguinal glands show central caseation. The spleen is enlarged and mottled with tiny gray tubercles. No other evidence of disease is found.

Guinea-pig 212. Well nourished, weight 275 gm., gain of weight 12 gm. There is a small caseating abscess in the left groin, and the regional lymph glands are swollen, and have caseous centers. The spleen is enlarged and studded with gray tubercles, 1 to 1.5 mm. in diameter. The other viscera appear normal.

Guinea-pig 213. Under nourished, weight 240 gm., loss of weight 20 gm. There is a large caseating mass of glands in the left inguinal fossa. The lungs are congested and scattered through them are many miliary tubercles. The spleen is similarly affected. The other organs are uninvolved.

Guinea-pig 214. Under nourished. Weight 210 gm., loss of weight 25 gm. There is a large caseating abscess in the left groin and the regional lymph glands are enlarged and softened. The lungs and the spleen show numerous gray tubercles.

Guinea pig 215. Emaciated, weight 119 gm., loss of weight 40 gm. There is an abscess in the left groin and the regional inguinal and iliac lymph nodes are soft and necrotic. All the viscera appear normal, except the spleen, which is mottled with gray tubercles.

Guinea-pig 216. Emaciated, weight 185 gm., loss of weight 45 gm. There is no reaction at the site of injection, but there is a central caseating plug in the center of one of the left inguinal lymph nodes. The spleen shows numerous gray tubercles. Otherwise no tuberculosis is manifest.

Guinea-pig 217. Emaciated, weight 200 gm., loss of weight 40 gm. There is a caseating abscess in the left inguinal fossa and the spleen shows numerous miliary tubercles. There is no tuberculous involvement of the other organs.

Guinea-pig 218. Under nourished, weight 240 gm., loss of weight 15 gm. There is no local abscess in the groin, but the adjacent lymph glands have caseating centers. There are numerous small tubercles in the spleen.

Guinea-pig 219. Well nourished, weight 245 gm. In the left inguinal region the glands are softened and have central caseating plugs. No other evidence of tuberculosis found.

Guinea-pig 220. Well nourished, weight 255 gm., gain of weight 15 gm. There are two small caseating lymph nodes in the left groin. The spleen shows a few gray tubercles scattered through its pulp. The other viscera appear normal.

Guinea-pig 221. Well nourished, weight 270 gm., gain of weight 15 gm. The inguinal and the iliac lymph glands on the left side are necrotic. The spleen is mottled with gray tubercles. The other viscera appear normal.

TABLE I

Guinea-pig No.	Preliminary treatment	Duration of life after infection	Tuberculosis					Remarks
			Lungs	Liver	Spleen	Kidneys	Local	
202	<i>Tuberculo-protein</i>	<i>Dose</i>						
203	15 mgm.	45	+	+	+	+	+	
204	do.	49	+	+	+	+	+	
205	do.	52	+	+	+	+	+	Intercurrent infection
206	do.	52	+	+	+	+	+	
207	do.	53	+	+	+	+	+	
208	None	45	+	+	+	+	+	
209	do.	49	+	+	+	+	+	
210	15 mgm.	55	+	+	+	+	+	Well nourished
211	do.	56	+	+	+	+	+	
212	do.	55	+	+	+	+	+	
213	do.	55	+	+	+	+	+	Well nourished
214	do.	55	+	+	+	+	+	Well nourished
215	do.	55	+	+	+	+	+	
216	do.	55	+	+	+	+	+	Well nourished
217	do.	55	+	+	+	+	+	
218	do.	55	+	+	+	+	+	
219	do.	55	+	+	+	+	+	Well nourished
220	do.	55	+	+	+	+	+	
221	do.	55	+	+	+	+	+	
222	do.	55	+	+	+	+	+	
223	do.	55	+	+	+	+	+	Well nourished
224	None	55	+	+	+	+	+	Well nourished
225	do.	55	+	+	+	+	+	Well nourished
226	do.	55	+	+	+	+	+	
227	do.	55	+	+	+	+	+	
228	do.	55	+	+	+	+	+	
229	do.	55	+	+	+	+	+	Well nourished
230	do.	55	+	+	+	+	+	Well nourished
231	do.	55	+	+	+	+	+	Well nourished
* Died. † Etherized.								



Guinea-pig 27. Well nourished, weight 295 gm., gain of weight 40 gm. No abscess is found in the groin but the left inguinal lymph glands are necrotic. There are no signs of tuberculosis in the viscera.

Guinea-pig 28. There is a large soft abscess in the left inguinal region, and a few yellow tubercles, 3 mm. in diameter in the lungs and in the spleen.

Guinea-pig 29. Well nourished, weight 280 gm., gain of weight 20 gm. There is a large abscess in the left inguinal fossa and the regional lymph glands are necrotic. A few yellow tubercles, 3 mm. in diameter, are seen in the lungs and spleen.

Guinea-pig 30. Emaciated, weight 230 gm., loss of weight 20 gm. There is no abscess in the groin but the inguinal lymph glands are caseous. The lungs are congested and edematous, but there is no macroscopic tuberculosis. The spleen shows numerous gray and yellow tubercles.

Guinea-pig 31. Well nourished, weight 300 gm., gain of weight 40 gm. There is a small caseous abscess in the left inguinal region and the lymph nodes are necrotic. A few yellow tubercles are seen in the lungs and in the spleen.

Guinea-pig 32. Well nourished, weight 300 gm., gain of weight 35 gm. There is a small caseating abscess in the left groin and the regional lymph glands are caseous. Aside from numerous gray tubercles in the spleen, there is no evident tuberculosis.

Guinea-pig 33. Emaciated, weight 205 gm., loss of weight 30 gm. The left inguinal lymph nodes are caseous. There is an acute bronchitis and peribronchitis, but no tubercles are seen in the lungs. The spleen is small, but riddled with gray and yellow tubercles. There is evident enlargement of the mesenteric lymph glands.

Guinea-pig 34. Emaciated, weight 200 gm., loss of weight 25 gm. There are enlarged caseating lymph nodes in the left groin. The lungs show numerous caseating tubercles and a few which have undergone fibrosis. There are also numerous yellow tubercles in the spleen.

Guinea-pig 35. Well nourished, weight 230 gm., loss of weight 10 gm. The lymph glands in the left inguinal region are large and necrotic. Numerous gray and yellow tubercles are seen throughout the lungs and the spleen. The other viscera appear normal.

Control non-sensitized guinea-pigs, 222 to 232, etherized on the seventieth day after infection, for a comparison of the lesions with those found in the foregoing sensitized animals.

Guinea-pig 222. Well nourished, weight 290 gm., gain of weight 30 gm. There is a small abscess in the left groin and numerous tiny gray tubercles are seen in the spleen. The other viscera are uninvolved.

Guinea-pig 223. Well nourished, weight 310 gm., gain of weight 40 gm. There is a caseating abscess in the left groin but there is no evident tuberculosis of any of the viscera.

Guinea-pig 224. Well nourished, weight 315 gm., gain of weight 45 gm. The lymph glands in the left groin are caseous. Numerous gray tubercles are seen throughout the lungs and the spleen is mottled with gray and yellow nodules.

Guinea-pig 225. Under nourished, weight 240 gm., loss of weight 30 gm. There is no abscess in the groin, but the inguinal and the iliac lymph glands show central plugs of caseation. There are numerous miliary tubercles scattered throughout the lungs and the spleen is mottled with gray and yellow tubercles.

Guinea-pig 226. Emaciated, weight 200 gm., loss of weight 40 gm. There is a small caseating abscess in the left groin, with necrotic regional lymph nodes. There are numerous gray tubercles throughout the lungs and the spleen, several of which are undergoing softening.

Guinea-pig 227. Emaciated, weight 225 gm., loss of weight 30 gm. The inguinal and the iliac lymph glands are necrotic. There

are no tubercles to be seen in the lungs or in any of the viscera except in the spleen, in which a few large yellow tubercles, 2.5 mm. in diameter, are seen.

Guinea-pig 228. Emaciated, weight 190 gm., loss of weight 40 gm. There are necrotic caseating lymph nodes in the left groin and the spleen is distorted by numerous yellow, softened tubercles. Otherwise the viscera are uninvolved.

Guinea-pig 229. Emaciated, weight 205 gm., loss of weight 42 gm. There is a small caseating lymph gland in the left groin, with infiltration of the adjacent muscles. The lungs show an acute broncho-pneumonia, and peribronchitis. The spleen is small and studded with gray tubercles. The mesenteric lymph nodes are swollen but are not necrotic.

Guinea-pig 230. Under nourished, weight 205 gm., loss of weight 30 gm. There is no local reaction in the left groin, except central caseation of the inguinal lymph glands. There are numerous gray, and a few yellow tubercles throughout the lungs, and the spleen is riddled with gray tubercles, 1 mm. in diameter.

Guinea-pig 231. Emaciated, weight 200 gm., loss of weight 25 gm. The left inguinal lymph nodes are necrotic and there is a caseating abscess involving the deep structures of the thigh. The lungs are dotted with large tubercles, 0.5 to 1.5 mm. in diameter, which show central caseation. The spleen is enlarged and studded with yellow tubercles. The mesenteric lymph nodes are swollen.

Guinea-pig 232. Emaciated, weight 195 gm., loss of weight 35 gm. There are central caseous plugs in the left inguinal and iliac lymph glands. There is no tuberculosis evident in any of the viscera except the spleen, which shows numerous small yellow tubercles.

TABLE II

Guinea-pig No.	Preliminary treatment	Duration of infection	Tuberculosis					Remarks
			Lungs	Liver	Spleen	Kidneys	Local	
25	15 mgm.	70	+	+	+	+	+	Well nourished
26		70	+	+	+	+	+	
27		70	+	+	+	+	+	
28		70	+	+	+	+	+	
29		70	+	+	+	+	+	Well nourished
30		70	+	+	+	+	+	
31		70	+	+	+	+	+	
32		70	+	+	+	+	+	
33		70	+	+	+	+	+	Well nourished
34		70	+	+	+	+	+	
35		70	+	+	+	+	+	
222	None	70	+	+	+	+	+	Well nourished
223		70	+	+	+	+	+	
224		70	+	+	+	+	+	
225		70	+	+	+	+	+	
226		70	+	+	+	+	+	Well nourished
227		70	+	+	+	+	+	
228		70	+	+	+	+	+	
229		70	+	+	+	+	+	
230		70	+	+	+	+	+	Well nourished
231		70	+	+	+	+	+	
232		70	+	+	+	+	+	

\* Etherized.

C.

Sensitized guinea-pigs 60 to 65 and 72 to 77, inclusive, infected January 9 and control non-sensitized guinea-pigs 260 to 275, inclusive, in which the disease had existed the same length of time, were etherized one hundred and fifty-seven days later, on June 15.

Guinea-pig 60. Well nourished, weight 230 gm., gain of weight 10 gm. There is a small abscess in the left groin and the associated inguinal lymph glands are necrotic. The spleen is riddled with gray tubercles. The other viscera are apparently uninvolved.

Guinea-pig 61. Emaciated, weight 195 gm., loss of weight 30 gm. There is a large caseating abscess in the left inguinal fossa

and the regional lymph nodes are softened. The lungs are studded with numerous yellow tubercles, about many of which there is a zone of fibrous tissue but there is no cavity formation. The spleen is enlarged and distorted by caseating tubercles. There are a few gray tubercles in the cortex of each kidney.

Guinea-pig 62. Emaciated, weight 200 gm., loss of weight 40 gm. The lungs are voluminous and throughout them there are numerous softened yellow tubercles. There are many miliary tubercles in the spleen and in the kidneys.

Guinea-pig 63. Emaciated, weight 200 gm., loss of weight 35 gm. There is a necrotic abscess in the left groin and the neighboring lymph glands are necrotic. The lungs and the spleen show very numerous gray and yellow tubercles. None of the other viscera are diseased.

Guinea-pig 64. Emaciated, weight 185 gm., loss of weight 50 gm. There is a fluctuating abscess in the left inguinal fossa and the inguinal and iliac lymph glands on this side are caseous. The lungs show numerous caseating tubercles and two small cavities. The spleen is much enlarged and studded with gray and yellow tubercles.

Guinea-pig 65. Emaciated, weight 220 gm., loss of weight 40 gm. The lungs are voluminous and show small areas of consolidation, with many tubercles. The spleen is enlarged and throughout its parenchyma are numerous small tubercles.

Guinea-pig 72. Well nourished, weight 220 gm., loss of weight 15 gm. There is a small abscess in the left groin, and central plugs of caseation are seen in the regional lymph glands. The spleen shows numerous gray and yellow tubercles. Otherwise there is no evidence of the disease in the viscera.

Guinea-pig 73. Under nourished, weight 240 gm., loss of weight 10 gm. The inguinal and the iliac lymph nodes are softened and necrotic. The lungs and the other viscera, with the exception of the spleen, show no tuberculous involvement. The spleen is much enlarged, firm, and scattered through it are very numerous yellow and gray tubercles.

Guinea-pig 74. Well nourished, weight 250 gm. No change in weight since the time of inoculation. The inguinal and the iliac lymph nodes on the left side are small, fibrous and show central necrotic plugs. The spleen is enlarged and shows fairly numerous yellow and gray tubercles. There are no tubercles seen in the lungs or in the other viscera.

Guinea-pig 75. Emaciated, weight 205 gm., loss of weight 43 gm. There is a small abscess in the left groin and the associated lymph nodes are necrotic. There are a few large yellow tubercles and numerous miliary tubercles scattered through the lungs and the spleen.

Guinea-pig 76. Well nourished, weight 235 gm., gain of weight 5 gm. The inguinal and the iliac lymph nodes show central necrosis. The spleen is enlarged and in its parenchyma numerous small yellow and gray tubercles are visible. No tuberculous involvement of the other internal organs is seen.

Guinea-pig 77. Emaciated, weight 211 gm., loss of weight 19 gm. The left inguinal and iliac lymph nodes are completely necrotic. The spleen is much enlarged and distorted by numerous yellow tubercles. The other viscera, aside from cloudy swelling, appear normal.

#### CONTROLS.

Guinea-pig 260. Emaciated, weight 204 gm., loss of weight 28 gm. The lymph nodes in the left inguinal fossa are caseous. The spleen is enlarged, firm, and mottled with large gray tubercles. The other viscera are uninvolved in the process.

Guinea-pig 261. Under nourished, weight 230 gm., loss of weight 12 gm. There is a suppurating abscess in the left inguinal fossa, where the glands are necrotic and softened. There is no evidence of tuberculosis except in the spleen, where numerous gray tubercles are scattered through the parenchyma.

Guinea-pig 262. Emaciated, weight 208 gm., loss of weight 22 gm. There is no abscess in the left groin but there is a central plug of caseation in one of the left inguinal lymph glands. The spleen is the only organ in which evident tuberculosis is manifest, and it is distorted by many yellow and gray tubercles.

Guinea-pig 263. The left inguinal and iliac lymph glands show fibrosis and central caseation. There is no tuberculous involvement of any of the viscera except the spleen, throughout which many caseating tubercles are seen.

Guinea-pig 264. Well nourished, weight 255 gm., gain of weight 15 gm. The inguinal and the iliac lymph nodes on the left are partially necrotic. The spleen is enlarged and scattered through it are many fresh and caseous tubercles.

Guinea-pig 265. Emaciated, weight 22 gm., loss of weight 38 gm. The left inguinal and iliac lymph glands are swollen and partially necrotic; the spleen is enlarged and firm, and shows many gray tubercles.

Guinea-pig 270. Well nourished, weight 270 gm., gain of weight 20 gm. There is a small caseating abscess in the left inguinal region and the regional lymph nodes show central necrosis. The spleen and the lungs show fairly numerous caseating tubercles.

Guinea-pig 271. Under nourished, weight 230 gm., loss of weight 18 gm. There is a necrotic plug in one of the left inguinal lymph nodes. The spleen is enlarged and distorted by numerous yellow tubercles. No other tuberculous involvement found.

Guinea-pig 272. Well nourished, weight 260 gm., gain of weight 5 gm. Aside from a small abscess in the left iliac region and numerous gray tubercles throughout the spleen, the viscera are normal.

Guinea-pig 273. Emaciated, weight 212 gm., loss of weight 38 gm. There are numerous tubercles scattered throughout the spleen; otherwise no evidence of tuberculosis is found.

Guinea-pig 274. Well nourished, weight 255 gm., gain of weight 3 gm. There is a small caseating abscess in the left groin, with necrosis of the associated lymph glands. No visceral tuberculosis is found except in the spleen, where there are many gray and yellow tubercles.

Guinea-pig 275. Emaciated, weight 215 gm., loss of weight 25 gm. There is necrosis of the iliac lymph nodes and a few gray tubercles are scattered throughout the lungs. The spleen is enlarged, firm, and distorted by numerous large caseating tubercles.

TABLE III

Guinea-pig No.	Preliminary treatment	Duration of infection in weeks	Tuberculosis					Remarks
			Lungs	Liver	Spleen	Kidneys	Local	
60	Tuberculin protein	15	+	15	+	+	+	Well nourished
61	do.	+	15	+	+	+	+	
62	do.	+	15	+	+	+	+	
63	do.	+	15	+	+	+	+	
64	do.	+	15	+	+	+	+	
65	do.	+	15	+	+	+	+	
72	do.	+	15	+	+	+	+	Well nourished
73	do.	+	15	+	+	+	+	
74	do.	+	15	+	+	+	+	Well nourished
75	do.	+	15	+	+	+	+	
76	do.	+	15	+	+	+	+	Well nourished
77	do.	+	15	+	+	+	+	
261	None	+	15	+	+	+	+	
262	do.	+	15	+	+	+	+	
263	do.	+	15	+	+	+	+	
264	do.	+	15	+	+	+	+	Well nourished
265	do.	+	15	+	+	+	+	
270	do.	+	15	+	+	+	+	Well nourished
271	do.	+	15	+	+	+	+	
272	do.	+	15	+	+	+	+	Well nourished
273	do.	+	15	+	+	+	+	
274	do.	+	15	+	+	+	+	Well nourished
275	do.	+	15	+	+	+	+	

+ Etherized.

The evidence furnished by this series of experiments also was definite, and it was quite clear that sensitization with a tuberculo-protein had definitely diminished the resistance of the animals to infection with living bacilli of the human type. Mindful of the fact that tuberculous animals, though immune to reinfection with small numbers of bacilli, are less resistant to reinfection with larger numbers of the organisms, a second series of sensitized guinea-pigs, with a parallel series of control animals, were infected with smaller doses of the strain of tubercle bacilli used in the preceding experiments.

### SERIES III.

January 10, 1912. Ten guinea-pigs, 81-90, were sensitized by the intraperitoneal injection of 15 mgm. of tuberculo-protein; twenty-four days later, on February 3, these animals, together with ten non-sensitized guinea-pigs, received subcutaneously, in the tissues of the left groin, 0.1 ccm. of a suspension of *H<sub>a</sub>*, which contained one organism in every two fields of the oil immersion lens. Eighty-five days after inoculation, on April 29, all twenty animals were etherized, sectioned, and the lesions compared.

#### SENSITIZED GUINEA-PIGS 81-90.

Guinea-pig 81. Emaciated, weight 210 gm., loss of weight 43 gm. There is a small caseous abscess in the left inguinal region, with necrosis of the associated lymph glands. The lungs show a most striking picture; they are hyperemic and mottled with large yellow plaques of caseation. The mediastinal lymph glands are large and firm. The spleen is not enlarged and shows relatively few gray tubercles. The other viscera are uninvolved.

Guinea-pig 82. Emaciated, weight 205 gm., loss of weight 38 gm. There are enlarged inguinal and iliac lymph glands on the left side that show central caseation. The lungs are pale and translucent, and dotted with yellow tubercles. The spleen is enormously enlarged, the pulp increased, and studded with yellow tubercles. The mesenteric lymph nodes are swollen.

Guinea-pig 83. Fairly well nourished, weight 240 gm., loss of weight 15 gm. The glands in the left groin are necrotic and there is infiltration of the adjacent muscle. The lungs show numerous gray and yellow tubercles. The spleen is small and studded with gray tubercles.

Guinea-pig 84. Under nourished, weight 205 gm., loss of weight 23 gm. There is a large caseating abscess in the left groin, with caseous adjacent lymph glands. There are a few yellow tubercles in the spleen. Otherwise the internal organs appear normal.

Guinea-pig 85. Emaciated, weight 203 gm., loss of weight 20 gm. There is a small caseating abscess in the left groin, with necrosis of the iliac lymph glands. Except for large yellow caseous tubercles throughout the spleen, the viscera are uninvolved.

Guinea-pig 86. Well nourished, weight 310 gm., gain of weight 50 gm. There is beginning caseation of the lymph nodes and a necrotic abscess in the left inguinal fossa. There are numerous gray tubercles throughout the lungs and the spleen.

Guinea-pig 87. Well nourished, gain of weight 15 gm. There is a large abscess in the left groin, with coagulation necrosis of the inguinal and of the iliac lymph nodes. There are a few yellow and gray tubercles in the spleen, and marked congestion of the other viscera.

Guinea-pig 88. Emaciated, loss of weight 40 gm. There is no macroscopic tuberculosis, except in the left inguinal lymph glands, which are necrotic, and in the spleen, which is mottled with yellow and gray tubercles.

Guinea-pig 89. Well nourished, weight 250 gm. Weight stationary since injection. The left inguinal and iliac lymph glands are slightly enlarged and fibrous. There are numerous gray tubercles throughout the parenchyma of the spleen. Otherwise the viscera appear normal.

Guinea-pig 90. Well nourished, weight 290 gm., gain of weight 18 gm. A small caseating abscess and several large caseating lymph glands are seen in the left inguinal fossa. There are numerous tubercles scattered through the spleen.

#### CONTROL GUINEA-PIGS 280-290.

Guinea-pig 280. Well nourished, weight 290 gm., gain of weight 20 gm. There is a small fluctuating abscess in the left groin and a marked swelling of the adjacent lymph glands, some of which show central caseation. All of the viscera appear normal except the spleen, which is mottled with numerous gray tubercles.

Guinea-pig 281. Well nourished, weight 300 gm., gain of weight 45 gm. (pregnant). There is a small caseating abscess in the left groin and the adjacent lymph glands are necrotic. The lungs show no evidence of tuberculosis. The spleen is somewhat enlarged and distorted by numerous gray tubercles.

Guinea-pig 282. Well nourished, weight 260 gm., gain of weight 12 gm. The lymph glands in the left inguinal fossa are caseous and there are a few gray tubercles scattered throughout the spleen. Otherwise no evidence of tuberculous involvement is apparent.

Guinea-pig 283. Well nourished, weight 275 gm., unchanged since infection. The inguinal and the iliac lymph nodes on the left are fibrous and show central caseation. There are numerous gray tubercles in the parenchyma of the spleen.

Guinea-pig 284. Well nourished, weight 285 gm., gain of weight 26 gm. (pregnant). There is a small suppurating abscess in the left groin. The adjacent lymph nodes are necrotic and there are numerous yellow and a few gray tubercles in the spleen.

Guinea-pig 285. Well nourished, weight 285 gm., gain of weight 12 gm. The left inguinal and iliac lymph glands are small and show central necrosis. A few fresh gray tubercles are seen in the lungs and numerous older tubercles are scattered throughout the spleen.

Guinea-pig 286. Emaciated, weight 245 gm., loss of weight 7 gm. There is a small abscess in the left groin and the adjacent lymph glands are swollen and infiltrated. The spleen is enlarged, firm and mottled with gray tubercles.

Guinea-pig 287. Well nourished, weight 272 gm., gain of weight 14 gm. There is no abscess in the left groin, but the inguinal and the iliac lymph nodes are softened and necrotic. The spleen is slightly enlarged, very firm and throughout it are numerous yellow tubercles.

Guinea-pig 288. Weight 250 gm., loss of weight 18 gm. The inguinal and the iliac lymph nodes are softened and caseous. Except for numerous gray tubercles throughout the spleen, the other internal organs appear normal.

Guinea-pig 289. Emaciated, weight 228 gm., loss of weight 39 gm. The inguinal lymph nodes on the left side show central necrosis and there are numerous yellow tubercles in the spleen.

Guinea-pig 290. Well nourished, weight 265 gm., gain of weight 8 gm. There is a small caseating abscess in the left groin and the regional lymph glands are fibrosed. No evidence of tuberculosis is visible in the viscera.





TABLE V

Guinea-pig No.	Preliminary treatment	Duration of life after infection	Tuberculosis				Remarks
			Lungs	Liver	Spleen	Kidneys	
	<i>Tuberculo-protein</i>	<i>Days</i>					
95	44 mgm.	+ 75	—	—	+	—	Well nourished
96	do.	+ 75	—	—	—	—	Well nourished
97	do.	+ 75	—	—	—	—	Well nourished
98	do.	+ 75	—	—	+	—	Well nourished
99	do.	+ 75	—	—	—	—	Well nourished
100	do.	+ 75	—	—	—	—	Well nourished
101	do.	+ 75	+	—	+	—	Well nourished
103	do.	+ 75	+	—	+	—	Pregnant
293	None	+ 75	—	—	—	—	Well nourished
294	do.	+ 75	—	—	—	—	Well nourished
295	do.	+ 75	—	—	—	—	Pregnant
296	do.	+ 75	—	—	—	—	Well nourished
297	do.	+ 75	—	—	—	—	Well nourished
299	do.	+ 75	—	—	—	—	Well nourished
300	do.	+ 75	—	—	—	—	Well nourished
302	do.	+ 75	—	—	—	—	Well nourished
303	do.	+ 75	—	—	—	—	Well nourished

† Etherized.

In this experiment very little difference is to be noted in the extent of the disease in the sensitized and in the non-sensitized animals. In seven of the hypersensitive animals the spleen was involved; in only one were the lungs diseased and in one the infection remained strictly localized, whereas in the control, non-sensitized animals, in five the disease did not spread beyond the spleen, in two the lungs were involved and in two there was a localization of the process in the glands draining the site of inoculation. In short, the resistance of the animals that were sensitized was unchanged, or perhaps slightly increased.

Thus far, for the sake of completeness, the detailed findings in each set of experiments have been recorded; but for the sake of brevity, in the following experiments, details will be given only when omission of them would fail to bring out the salient points of the work.

## INFLUENCE OF THE REFRACTORY STATE UPON INFECTION.

## SERIES V.

April 25, 1912. Five guinea-pigs, 114 to 118, inclusive, twenty-three days after the intraperitoneal injection of 14 mgm. of tuberculo-protein, were given a sublethal intravenous injection of 8 mgm. of the same preparation. Within two to four hours after the administration of the intoxicating dose, and while they still showed the symptoms of anaphylactic shock, these animals, together with five untreated non-sensitized controls (guinea-pigs 309 to 315) were each given 0.15 ccm. of a salt solution suspension of *Ha*, which contained two bacilli in every three fields of the oil immersion lens. Seventy-three days later (June 7) all of these animals were etherized and examined.

In all five of the intoxicated animals, the lungs and the spleen were involved in an acute miliary tuberculosis, and many of the lesions showed beginning caseation, whereas in only two of the controls had the disease invaded the lungs.

These findings are in accord with those of Krause, that refractory animals are less resistant to infection than are sensitized or non-sensitized animals. The lowering of resistance by shock, however, is not entirely specific, for while in this

condition several other guinea pigs (118 to 122) succumbed to doses of virulent typhoid bacilli, which were not lethal, to untreated non-sensitized control animals.

TO TEST THE INFLUENCE OF INHERITED HYPERSENSITIVENESS TO A TUBERCULO-PROTEIN UPON INFECTION WITH *BACILLUS TUBERCULOSIS*.

## SERIES VI.

Twelve guinea-pigs, from twenty to forty days old, varying in weight from 105 to 190 gm. the offspring of actively sensitized mothers, and twelve guinea-pigs of the same age and about the same weight, born of non-sensitized, normal females, were used in this series.

## A.

February 14, 1912. Five guinea-pigs with inherited hypersensitiveness to tuberculo-protein, together with seven normal young guinea-pigs, were injected into the subcutaneous tissues of the left groin, with 0.5 ccm. of a suspension of *Ha* in salt solution, which contained one bacillus in each field of the oil immersion lens.

On May 1, seventy-five days later, these animals were etherized, sectioned, and the lesions compared.

In three of the animals with inherited hypersensitiveness, there was, in addition to caseation at the site of inoculation, miliary tuberculosis of the lungs and spleen, whereas in the controls, the disease had involved no internal organ except the spleen. In two of the animals with inherited hypersensitiveness, and in two of the controls, there was a small abscess in the left inguinal region, with caseation of the regional lymph glands and numerous gray tubercles in the spleen.

## B.

April 3. Seven guinea-pigs with inherited hypersensitiveness to tuberculo-protein and seven normal young guinea-pigs, were each given a subcutaneous injection into the left groin of the same amount of tubercle bacilli as was administered to the animals in Series A. They were all etherized on June 17 and the lesions compared.

In four of the sensitive animals, there was extensive tuberculosis of the lungs and spleen, with beginning caseation of the lesions, whereas the corresponding control animals showed caseation of the inguinal and iliac lymph glands and gray tubercles throughout the spleen, but no involvement of the lungs. In three of the sensitive guinea-pigs there was no further advance of the process than in the corresponding controls.

In this series, inherited hypersensitiveness to our tuberculo-protein brought about a diminution in the resisting power of the animals to infection by tubercle bacilli, just as in many instances the active sensitization did in the experiments already cited.

The diminished resistance to tuberculosis shown by the animals with inherited allergy, offers a possible explanation for the increased susceptibility to infection of the offspring of tuberculous mothers; and although it is unwise to hazard

speculation as to the cause of the great incidence of tuberculosis among the children of infected parents, still, in a certain small proportion of the cases, a similar mechanism may play some rôle.

A study of the resistance of animals in the preanaphylactic state to infection with tubercle bacilli cannot now be recorded, inasmuch as the animals in this series became infected with an acute intercurrent entero-colitis and were not available for study.

#### HYPERSENSITIVENESS TO A TUBERCULO-PROTEIN AND INFECTION WITH *BACILLUS TUBERCULOSIS*.

##### RABBIT EXPERIMENTS.

Inasmuch as rabbits are relatively insusceptible to infection with the human type of bacillus tuberculosis, developing a slow chronic disease lasting months and unattended by a period of dyspnea, it was of interest to note if the course of the disease produced in them could be essentially modified by sensitization with a tuberculo-protein. In the following series of animals, it will be seen that some were treated with one large dose of the protein, others received several smaller doses at three-day intervals, and all were inoculated with tubercle bacilli about twenty days after the intraperitoneal sensitizing dose. For each sensitized animal, a control, untreated, of about equal weight and of the same age, sex and color, was used. All were caged together and kept under as nearly identical conditions as possible. In all instances, the suspensions of tubercle bacilli were prepared as already described, and the same substance was used to bring about the hypersensitive state.

December 14, 1911. Rabbit 5, white female, weight 2400 gm. Intraperitoneal injection of 80 mgm. of tuberculo-protein.

January 9, 1912. Intravenous injection into the lateral ear vein of 2 ccm. of a salt solution suspension of *Ha*, containing 0.4 mgm. of bacilli. This suspension was about one-half the density of a twenty-four hour broth culture of typhoid bacilli.

On January 19 there was dyspnea, which lasted for three days, followed by apparent recovery. Six days later, there was evident wasting and the animal looked ill. On February 19 the rabbit was found dead in its cage.

*Autopsy*.—Emaciated, weight 1220 gm. No reaction at the site of inoculation. The lungs are voluminous and the pleura is studded with tiny gray and yellow nodules, up to 1.5 mm. in diameter. The lungs are congested and show patches of gelatinous consolidation and innumerable gray and yellow tubercles, 1 to 1.5 mm. in size. There is also a marked acute bronchitis.

The spleen is not enlarged and no tubercles are seen in it or in the liver. The peritoneum is smooth and glistening. The kidneys are congested and firm, and scattered through the cortex and pyramids are several miliary tubercles. The lymph glands are not enlarged or caseous.

Microscopic examination shows numerous acid-fast bacilli in the lungs. The tubercles in the lungs show numerous epithelial and giant cells and in most areas a central zone of coagulative necrosis. In the kidneys there are a few typical young tubercles.

January 11, 1912. Rabbit 6, white female, weight 2325 gm. Intraperitoneal injection of 75 mgm. of tuberculo-protein.

February 12. Intravenous injection into the lateral ear vein of 2 ccm. of a salt solution suspension of *Ha*, containing 0.28 mgm. of bacilli and 2 ccm. of the same suspension subcutaneously in the left groin.

On the 16th of February, at the site of inoculation, there was a firm, yellow nodule, 1½ cm. in diameter, and two smaller nodes near the base of the ear. On February 20 these nodules had become larger and were white and fluctuating. On February 22 several new nodules, 4 cm. from the site of inoculation, appeared. (On this day the animal gave birth to a litter of four young.)

February 24. There was marked dyspnea and the animal was visibly emaciated. The dyspnea persisted until the 6th of March when there was practically air hunger, emaciation and cyanosis. The nodules in the ear had now almost disappeared. The pus made from one of the nodules shows numerous acid-fast bacilli.

March 20. Animal died at 10 a. m. Weight 1170 gm.

*Autopsy*.—The lungs are very voluminous, do not collapse and are practically non-air containing. Both are deep red in color, mottled with yellow and the parenchyma contains many tubercles, 1 to 2 mm. in diameter, some of which show advanced caseation.

There are a few tubercles seen in the slightly enlarged spleen. The liver is apparently uninvolved. The kidneys are pale and mottled with fairly numerous gray nodules; those in the cortex spreading as linear rays through the pyramids. The peritoneum shows a few gray tubercles and very numerous miliary tubercles on the posterior abdominal wall. The nodules in the ear, already described, show dense fibrous walls and central caseation.

Microscopic examination of the spleen, lungs and kidneys shows typical tubercles, some of which are undergoing caseation.

January 11. Rabbit 7, gray female, weight 2265 gm. Intraperitoneal injection into the lateral ear vein of 2 ccm. of a salt solution suspension of *Ha*, which contained 0.28 mgm. of bacilli and simultaneously 2 ccm. of the same suspension into the tissues of the left groin. On February 16 there was a yellow nodule, 1 cm. in diameter, at the site of the intravenous injection. Four days later the nodule was enlarged and caseous and on the following day, two similar tumors appeared at the base of the ear. The animal was losing weight and on February 23 there was marked dyspnea, which became more intense and persisted until the 10th of March. It then became less marked, but there was a recurrence of dyspnea with tachypnea on March 24, which persisted until the death of the animal on the 4th of April.

*Autopsy*.—Weight 1290 gm. There are three caseating nodules in the left ear with yellow purulent contents, rich in acid-fast bacilli. The necrotic areas are well circumscribed and the cartilage beneath is eroded. The lungs are voluminous, reddish yellow in color and studded with tubercles 1 to 3 mm. in diameter. On section the parenchyma shows areas of broncho-pneumonia and numerous fresh and caseous tubercles, 0.5 to 2 mm. in diameter. There are no cavities seen. There is a marked secondary bronchitis and peribronchitis.

The liver is enlarged, but shows no definite involvement. The spleen is slightly swollen and soft. The peritoneum is clean. The kidneys are gray, swollen and firm with scattered tubercles in the cortex and medulla. In the left groin there is an enlarged and caseous lymph node.

Microscopic examination of the spleen, lungs and kidneys shows typical tubercles, with numerous giant cells and central caseation.

January 17, 1912. Rabbit 8, white male, weight 2260 gm. Intraperitoneal injection of 116 mgm. of tuberculo-protein. On February 12 the animal was given an intravenous injection into the lateral ear vein of 2 ccm. of a salt solution suspension of *Ha* which contained 0.28 mgm. of bacilli and 2 ccm. of the same suspension into the subcutaneous tissues of the left groin.

Three days later a firm subcutaneous nodule appeared at the site of the intravenous inoculation, and on February 19 it was tense, yellow and measured 13 mm. in diameter.

February 25. Two new tumors have developed at the base of the ear, 3 cm. from the site of the inoculation. All the nodules are now softened and necrotic and the animal is slightly dys-



ponetic. On March 5 the dyspnea was more intense, the rabbit was cyanotic and losing weight (2060 gm.). On March 6 the dyspnea was less marked and the nodules in the ear had ulcerated through the skin. March 17 the animal died at 10.25 a. m.

*Autopsy.*—Weight 1630 gm. There are three nodules in the left ear, at or near the site of intravenous inoculation, which are caseous and on section show a fibrous wall and an eroded cartilaginous base. The contents of the tumors show numerous acid-fast bacilli. The lungs are collapsed and riddled with gray and yellow tubercles, 2 to 4 mm. in diameter. Small areas are atelectatic and hyperæmic, showing patches of broncho-pneumonia and marked bronchitis.

The heart is dilated, the myocardium is pale and flabby and there is a fresh warty vegetation on the anterior cusp of the mitral valve. The kidneys are pale and firm and a few yellow tubercles are seen in the cortex. Otherwise there is no evident tuberculosis.

Microscopic examination shows numerous tiny fresh tubercles with numerous giant cells, scattered through the lungs, and caseous tubercles in the cortex of the kidneys.

January 7. Rabbit 9, gray female, weight 1100 gm. Intraperitoneal injection of 85 mgm. of tuberculo-protein.

February 12. Intravenous injection of 2 cc. of salt solution suspension of *Ha*, which contained 0.28 mgm. of bacilli and 2 cc. of the same suspension subcutaneously into the left groin. On the 15th of February a firm, elevated nodule, 0.5 cm. in diameter, appeared at the site of the intravenous injection, and five days later this had increased to 1.4 cm. in size. On the 24th of February the surface of this tumor was ulcerated and covered with a brown crust. The animal was dull, looked ill and was losing weight (weight 980 gm.). On February 29 there was marked lethargy, anorexia and intense dyspnea. March 1, animal died at 3 p. m.

*Autopsy.*—The local lesions in the ear show central caseous plugs surrounded by an infiltrated zone and the ulceration has extended into the aural cartilage. A smear made from the contents of this ulcer shows numerous acid-fast bacilli. The lungs collapse normally, are deep pink in color and show no macroscopic tubercles. There are no manifest lesions of tuberculosis in the serous cavities, in the viscera or in the glands. Microscopic examination showed fairly numerous fresh miliary tubercles in the lungs.

January 31. Rabbit 10, white female, weight 1730 gm. Intraperitoneal injection of 22 mgm. of tuberculo-protein.

February 3 and 5. Intraperitoneal injection of 33 mgm. of tuberculo-protein.

February 27. Intravenous injection into the lateral ear vein of 2 cc. of a salt solution suspension of *Ha*, which contained 0.3 mgm. of bacilli and a subcutaneous injection of 2 cc. of the same suspension beneath the skin of the left groin.

From the time of inoculation until the 4th of March there were no symptoms and no reaction was visible at the sites of injection. On that day slight dyspnea developed and a tiny papule,  $\frac{1}{8}$  cm. in diameter, was noted at the site of the intravenous inoculation. Except for slight dyspnea and a progressive loss of weight (weight 1420 gm. on the 18th of March), the animal appeared in fairly good condition.

On March 20 this animal was etherized, together with control rabbit No. 14 which had received a larger dose of bacilli sixteen days before this rabbit was infected.

*Autopsy.*—Weight 1540 gm. No reaction found at the sites of inoculation. The lungs collapse partially on opening the chest, but show a surface greatly distorted by firm prominences and deep depressions. The eminences are made up of numerous tubercles, from 1 to 6 mm. in diameter, and the depressed areas consist of collapsed lung parenchyma. On section the lungs are riddled with yellow and gray tubercles, varying greatly in size.

No extensive caseation, no large areas of consolidation and no cavities.

The liver is swollen but shows no macroscopic tuberculosis. The spleen is enlarged and soft with prominent Malpighian corpuscles and a few small yellow tubercles are seen. The kidneys are swollen, gray and the glomeruli stand out prominently. A few gray and yellow tubercles, 1 to 3 mm. in size, are seen through the capsule and, on section, these present as radiating rays through the kidney substance. The peritoneum is clean.

*NOTE.*—The picture here is in striking contrast to that seen in rabbit 14. The pulmonary involvement is incomparably greater, although both the infecting dose and the time elapsed since inoculation are less. The spleen, too, is more involved in this animal.

January 31. Rabbit 11, tan and white female, weight 1925 gm. Intraperitoneal injection of 22 mgm. of tuberculo-protein.

February 3. Intraperitoneal injection of 22 mgm. of tuberculo-protein.

February 5. Intraperitoneal injection of 33 mgm. of tuberculo-protein.

February 27. Intravenous injection into the lateral ear of 2 cc. of a salt solution suspension of *Ha*, which contained 0.3 mgm. of bacilli and at the same time 2 cc. of the same suspension beneath the skin of the left groin.

March 1. There is a small elevated nodule at the site of intravenous inoculation and two others proximal to it.

March 4. The animal is dyspneic and dull.

March 18. The dyspnea has ceased and the animal is in good condition. The nodule in the ear has increased in size, is soft and yellow.

September 19. Emaciated, lethargy and dyspnea have developed during the past week and the rabbit is rapidly losing ground.

October 1. The emaciation, torpor and dyspnea are extreme and there is a paralysis of the hind quarters.

October 5. Animal died.

*Autopsy.*—Emaciated rabbit, weight 1200 gm.

In the left ear, at the site of infection, there is a large, yellow caseous nodule, the contents of which are completely necrotic. The lungs are fairly voluminous, hyperæmic and much distorted by numerous yellow tubercles, many of which have coalesced to form caseous patches. The margins of the lungs are emphysematous. There are no cavities.

The kidneys are pale and swollen and in the cortex are several tubercles, pin head in size.

The other viscera show no macroscopic tuberculosis. (See *Note*, rabbit 15.)

Rabbit 12, gray male, weight 2075 gm. Received three sensitizing doses of tuberculo-protein, but died from an acute intercurrent infection before inoculation of tubercle bacilli.

February 12. Rabbit 13, non-sensitized, white female, weight 1240 gm. Intravenous injection into the lateral ear vein of 2 cc. of a salt solution suspension of *Ha*, which contained 0.28 mgm. of bacilli and 2 cc. of the same suspension subcutaneously into the left groin.

Until the 28th of February the animal remained in good condition except for a small loss of weight. At this time the animal developed snuffles with frequent paroxysms of sneezing and a tenacious nasal discharge. The respiratory distress and emaciation were progressive and on March 1 the animal was found dead in cage.

*Autopsy.*—Weight 970 gm., great emaciation. No sign of reaction at the sites of inoculation. The lungs are voluminous, do not collapse, but are still air-containing, and float in water. The pleural surfaces are dull and dotted with numerous gray and yellow nodules, 0.5 to 0.25 cm. in diameter. On section the lung surface is red, mottled with yellow and here and there

are zones of consolidation about the bronchi with many gray and yellow tubercles throughout.

No tubercles are found in any of the other viscera. Microscopic examination of sections of the lungs shows typical young and caseating tubercles and areas of polymorphonuclear infiltration. The giant cells here, however, are fewer in number than those seen in the sections of the sensitized animal.

February 12. Rabbit 14, white female, weight 1200 gm., non-sensitized control. Intravenous inoculation into the lateral ear vein of 2 ccm. of a salt solution suspension of Ha, containing 0.30 mgm. of bacilli and 2 ccm. of the same suspension subcutaneously into the left groin.

On February 22 three yellow nodules, 0.5 cm. in diameter, were visible at or near the site of the intravenous injection. These increased in size and a week later, the largest had ulcerated through the skin. At no time until May 20, when the animal was etherized, did any signs of respiratory distress develop, the only sign apparent being slight emaciation. On May 20 the animal was etherized in order to compare the lesions here present with those that had developed in sensitized rabbit 10.

*Autopsy.*—Weight 1380 gm. (pregnant). The lungs are hyperæmic and slightly edematous. At and near the upper pole of both upper lobes are several nodes, 1 to 4 mm. in diameter, which project above the general surface of the organs, are yellow in color and very firm on palpation. The rest of the parenchyma is air-containing and only a few small tubercles are seen.

There are no tubercles seen in any of the other organs. The uterus contains six embryos, about ten days of age.

Microscopic examination shows caseating tubercles in the upper lobes of the lungs, few in number and showing fewer giant cells than were seen in the tubercles in rabbit 10.

February 27. Rabbit 15, non-sensitized, white male, weight 1900 gm. Intravenous injection into the lateral ear vein of 2 ccm. of a salt solution suspension of Ha, which contained 0.3 mgm. of bacilli and at the same time 2 ccm. of the same suspension into the subcutaneous tissues of the left groin.

In the course of three weeks a small nodule appeared at the site of the intravenous inoculation, which soon ulcerated and finally healed. The animal remained in good condition until the week of September 1, when emaciation rapidly developed and the animal became dyspneic and dull. It died on October 15.

*Autopsy.*—Emaciated rabbit, weight 1200 gm. There is no reaction at the sites of inoculation.

The lungs are voluminous, do not collapse when the chest is opened, are everywhere adherent to the thoracic wall, and the dense fibrous pleural adhesions are broken with difficulty. The lungs themselves are hyperæmic and completely riddled with caseous areas, leaving little lung tissue to be seen. A large cavity almost replaces the left lower lobe, another, slightly smaller, is found in the right lower lobe and several smaller vomicae occur throughout the organs.

Except for the kidneys the other viscera show no tuberculosis and in the kidneys only a few small cortical lesions are found.

*NOTE.*—This is the most striking instance of cavity formation noted in any of our experimental animals. The pulmonary involvement is far greater than in the sensitized rabbit 11 and it is interesting that although the latter lived almost as long, no vomicae were found in the lungs.

February 27. Rabbit 16, non-sensitized, white male, weight 2250 gm. Intravenous injection into the lateral ear vein of 2 ccm. of a salt solution suspension of Ha, which contained 0.28 mgm. of bacilli and at the same time 2 ccm. of the same suspension beneath the skin of the left groin.

Until June 7 the animal looked well and was gaining weight, but it then became dull, fed poorly and showed beginning emaciation and on June 12 it was etherized.

*Autopsy.*—There is no local reaction at the site of the inoculations. The lungs are hyperæmic and thickly studded with gray and yellow tubercles, 1.5 to 3 mm. in size, but in large part are air-containing and still float in water. The pleural surfaces show many tubercles, although not so numerous as in the sensitized mate. There is parenchymatous degeneration of the other viscera, but no further macroscopic evidence of tuberculosis.

Microscopic examination shows typical tubercles throughout the lungs.

March 7. Rabbit 17, white female, weight 1930 gm. Intraperitoneal injection of 90 mgm. of tuberculo-protein.

March 30. Intravenous injection into the lateral ear vein of 0.5 ccm. of a salt solution suspension of Ha, which contained 0.07 mgm. of bacilli.

May 1. The animal is now emaciating and is slightly dyspneic. There is no reaction at the site of infection.

May 11. The dyspnea has ceased and the rabbit is in fairly good condition.

July 2. Etherized and sectioned for a comparison of the extent of the disease with that produced in the control rabbit 22.

*Autopsy.*—Under nourished rabbit, weight 1700 gm. There is no local reaction at the point of inoculation.

The lungs are voluminous with irregular surfaces distorted by elevations and depressions. Scattered through the parenchyma are many fresh gray tubercles and very numerous caseating yellow nodules from 1.5 to 5.5 mm. in diameter.

The kidneys are pale and there are fairly numerous small yellow cortical tubercles in both organs. The other viscera show no tuberculous involvement.

March 7. Rabbit 18, white female, weight 1720 gm. Intraperitoneal injection of 85 mgm. of tuberculo-protein.

March 30. Intravenous injection into the lateral ear vein of 0.5 ccm. of a salt solution suspension of Ha, which contained 0.07 mgm. of bacilli.

April 27. There is slight dyspnea and a slight loss of weight (1670 gm.).

June 2. Etherized.

*Autopsy.*—Emaciated rabbit, weight 1480 gm. There are numerous subpleural tubercles and throughout the parenchyma of both lungs there are innumerable yellow caseous nodules, some of which have coalesced to form necrotic plaques. A few of these show well-defined encapsulation. The spleen and the kidneys are swollen and both contain fairly numerous tiny tubercles. The other viscera show no tuberculous involvement.

March 7, 1912. Rabbit 19, white female, weight 1900 gm. Intraperitoneal injection of 95 mgm. of tuberculo-protein.

March 30. Intravenous injection into the lateral ear vein of 0.5 ccm. of a salt solution suspension of Ha, which contained 0.07 mgm. of bacilli.

April 1. There is no reaction at the site of inoculation, and no symptoms have developed.

May 4. Etherized and lesions compared with those found in rabbit 20, its control mate.

*Autopsy.*—Weight 1750 gm. There are no lesions in the ear. The lungs are partially collapsed and dotted here and there with large tubercles up to 0.5 cm. in diameter, several of which are caseous. The interstitial tissue is congested and edematous.

The liver is large and soft and shows no evident tuberculosis. The spleen is enlarged and shows a few gray tubercles. The kidneys show cloudy swelling, and numerous subcapsular gray tubercles. The retroperitoneal fat is very small in amount.

Microscopic examination of the spleen, the lungs and the kidneys shows typical tuberculosis.

March 30. Rabbit 20, white female, weight 1940 gm., non-sensitized control. Intravenous injection into the lateral ear vein of 0.5 ccm. of a salt solution suspension of Ha, which contained 0.07 mgm. of bacilli.

April 28. There is no evidence of a local reaction at the site of inoculation and no respiratory distress, but there is rapid emaciation and lethargy.

May 3. The emaciation is progressive, the animal is dull, has diarrhea, and looks more like an animal with coccidiosis than like those we have seen die of tuberculosis.

May 4. Dead in cage.

*Autopsy.*—Weight 1370 gm., emaciated. Lungs red and collapsed, studded with firm, gray tubercles up to 0.4 mm. in diameter, some umbilicated and fibrous. The peritoneal cavity contains numerous cysts, up to 1.25 cm. in size. The omentum is distorted by many cysts and a thick exudate, and the liver is mottled with fresh lesions of coccidiosis. There is no macroscopic tuberculosis of the liver, spleen, kidneys or lymph nodes.

Microscopic examination shows young and older tubercles in the lungs, the latter with beginning fibrosis at their periphery.

March 30. Rabbit 22, white female, weight 2030 gm., non-sensitized control. Intravenous injection into the lateral ear vein of 0.5 ccm. of a salt solution suspension of Ha, which contained 0.07 mgm. of bacilli.

July 2. Since inoculation there has been no evidence of a local reaction and no symptoms have developed. Etherized.

*Autopsy.*—Well nourished rabbit, weight 1810 gm. There is no reaction at the site of infection. The lungs show numerous caseous nodules from 2 to 14 mm. in diameter, a few of which are encapsulated. There are no fresh tubercles and there is no cavity formation. No tubercles are seen in any of the other viscera except in the kidneys, in which a few yellow cortical tubercles are found.

Note.—The pulmonary lesions in this animal are more advanced than in the sensitized mate, but the renal involvement is less marked.

March 20. Rabbit 23, white female, weight 1590 gm. Intraperitoneal injection of 80 mgm. of tuberculo-protein.

April 10. Intravenous injection into the lateral ear vein of 0.5 ccm. of a salt solution suspension of Ha, which contained 0.07 mgm. of bacilli. No reaction at the site of the intravenous inoculation, no symptoms other than progressive emaciation had developed from the time of inoculation until the animal was etherized, together with control rabbit 27, on May 18.

*Autopsy.*—Weight 1120 gm. The lungs are deep pink in color and show a surface much distorted with tubercles of all sizes, from a pin point to a pin head in diameter; some are fresh and gray, others yellow and caseating; none are fibrous. Everywhere the parenchyma is studded with tubercles between which the tissue shows congestion and edema.

The liver is swollen but shows no evident tuberculosis and only a few old lesions of coccidiosis. The spleen is enlarged, firm and contains many tubercles. The kidneys are congested and show numerous tiny gray and yellow subcapsular tubercles, which on section appear as linear rays through the cortex and the pyramids. The mesenteric lymph glands are slightly enlarged.

Microscopic examination of the lungs and of the kidneys shows typical tubercles with many giant cells.

Note.—The pulmonary involvement is greater than that shown by control rabbit 27, although both received the same infecting dose, were allowed to live the same number of days and were housed together in the same cage. The renal and the splenic lesions, too, are more extensive here than in the control.

March 20. Rabbit 24, white female, weight 1800 gm. Intraperitoneal injection of 80 mgm. of tuberculo-protein.

April 10. Intravenous injection into the lateral ear vein of 1 ccm. of a saline suspension of Ha, which contained 0.14 mgm. of bacilli.

June 18. No symptoms have developed and no local reaction has appeared at the site of inoculation since the animal was infected. Etherized.

*Autopsy.*—Well nourished female (pregnant) rabbit, with good panniculus. The lungs are fairly voluminous and for the most part air-containing, although riddled with firm tubercles, 1 to 2 mm. in size. The pleural surfaces are irregular, pink in color and mottled with yellow nodules. On section innumerable tubercles, 1 to 3 mm. in size, are seen in the collapsed parenchyma, a few of which are undergoing caseation. The liver is swollen, as is also the spleen, but in neither are tubercles visible. The kidneys show a striking picture. They are pale red in color, swollen and beneath the capsule many gray and yellow tubercles, 0.5 and 1.0 mm. in diameter are seen. On section the markings are clearly defined, and the cortical tubercles stand out sharply. The pelvis of the right kidney is greatly dilated. There is no glandular involvement.

Microscopic examination shows typical tuberculosis of the spleen, the lungs and the kidneys.

March 20. Rabbit 25, Maltese, with white face, female, weight 2050 gm. Intraperitoneal injection of 90 mgm. of tuberculo-protein.

April 10. Intravenous injection into the lateral ear vein of 1 ccm. of a salt solution suspension of Ha, which contained 0.14 mgm. of bacilli.

No symptoms developed in the animal and it was etherized on June 7 for a comparison of the lesions with those developed in control rabbit 28.

*Autopsy.*—Weight 1820 gm. The lungs show scarcely any normal parenchyma, the organs being completely riddled with tubercles, 0.5 to 1.5 mm. in diameter.

The spleen and the liver show no macroscopic tuberculosis. The kidneys are swollen and congested and a few subcapsular gray tubercles, pin head in size, are seen.

April 10. Rabbit 28, Maltese, with white paws, female, weight 1878 gm., non-sensitized control. Intravenous injection into the lateral ear vein of 1 ccm. of a salt solution suspension of Ha, which contained 0.14 mgm. of bacilli. From the time of inoculation until June 6 when the animal was found dead in its cage, no symptoms other than emaciation were noted.

*Autopsy.*—Weight 1570 gm. The lungs are collapsed and studded with many large yellow caseous tubercles, firmly walled off by dense fibrous tissue. The interstitial tissue is hyperæmic, but shows relatively few tubercles, as compared with the lungs of rabbit 25.

The liver is swollen and shows numerous fresh lesions of coccidiosis. The spleen is small and quite normal in appearance. The kidneys are swollen and congested, but show no macroscopic tubercles. The peritoneal cavity contains many parasitic cysts.

Note.—The lesions are slightly more extensive in rabbit 28 than in the control animal, although the difference is not so striking as that seen in other pairs. Perhaps the intercurrent coccidiosis in the control is responsible, to some extent, for the greater advance of the tuberculous process in it. The walling off and caseation of the lesions in the lungs of the control animal suggest a greater resistance to infection than does the milary involvement in the sensitized rabbit.

April 10. Rabbit 26, white male, weight 2050 gm., control, non-sensitized animal. Intravenous injection into the lateral ear vein of 1 ccm. of a salt solution suspension of Ha, which contained 0.14 mgm. of bacilli.

June 18. The animal is in good condition, and has shown no symptoms since the time of inoculation. Etherized, together with sensitized rabbit 24, for a comparison of the lesions.

*Autopsy.*—Weight 2005 gm. The lungs are voluminous and show a greater involvement, with a further advance of the lesions, than do the lungs of the sensitized mate. Although in great part air-containing, the parenchyma shows areas of gelatinous translucent consolidation with numerous tubercles, gray or yellow in color. These vary in size from 0.5 to 1.7 mm. and several of



the largest are completely necrotic. Some have a definite fibrous investment.

The liver, the spleen and the kidneys show no evidence of tuberculosis.

April 10. Rabbit 27, white female, weight 1850 gm., control, non-sensitized animal. Intravenous injection into the lateral ear vein of 0.5 ccm. of a salt solution suspension of Ha, which contained 0.07 mgm. of bacilli.

May 18. Etherized with its sensitized mate, rabbit 23.

*Autopsy.*—Weight 1400 gm. There is no reaction at the site of the intravenous inoculation. The lungs are pink in color, the pleural surfaces distorted by fairly numerous tubercles up to 2 mm. in size. Between these the parenchyma is hyperemic, but unlike the lungs of rabbit 23 does not show as much infiltration with tubercles. The contrast is striking for there is an incomparably greater advance of the infection in the sensitized animal than is seen here.

The liver is enlarged and congested but no tubercles are seen. The spleen is not enlarged and a few tiny tubercles are seen through the pulp. The kidneys show a few tubercles, pin point in size and gray in color. At the lower pole of the left kidney there is a large yellow patch of firm, yellow necrosis and there are some fresh lesions of coccidiosis in the mesentery.

Microscopic examination shows typical tubercles in the lungs, spleen and kidneys.

TABLE VI

Rabbit		Preliminary treatment	Infecting dose of tubercle bacilli	Duration of infection	Tuberculosis					Remarks
Number	Mate				Lungs	Liver	Spleen	Kidneys	Local	
5	..	Tuberculo-protein 80 mgm.	0.04	* 41	+++	—	—	+	—	Dyspnea after 10 days
6	..	75 mgm.	0.56	* 36	+++	—	—	++	+	Dyspnea after 12 days. Litter
7	16	do.	0.56	* 51	+++	—	—	++	+	Dyspnea after 11 days
8	..	116 mgm.	0.56	* 33	+++	—	—	+	+	Dyspnea after 13 days
9	13	85 mgm.	0.56	* 17	—	—	—	—	—	Dyspnea after 17 days
10	14	88 mgm.	0.60	* 32	+++	—	—	—	—	Slight dyspnea after 5 days
11	15	77 mgm.	0.60	* 220	+++	—	—	++	++	Dyspnea after 8 days
13	9	None	0.56	* 18	+++	—	—	—	—	Smitten (rabbit septicæmia)
14	10	do.	0.60	* 67	—	—	—	—	+	No dyspnea. Pregnant
15	11	do.	0.60	* 230	+++	—	—	—	+	Marked omeia formation
16	7	do.	0.56	* 105	—	—	—	—	—	No dyspnea
17	12	80 mgm.	0.07	* 94	+++	—	—	—	—	Slight dyspnea after 31 days
18	..	85 mgm.	0.07	* 94	+++	—	++	++	—	Dyspnea after 23 days
19	30	95 mgm.	0.07	* 35	++	—	—	+	—	No dyspnea
20	19	do.	0.07	* 35	++	—	—	—	—	Coccidiosis
21	17	do.	0.07	* 94	++	—	—	—	—	No dyspnea
22	17	do.	0.07	* 38	+++	—	—	++	—	No dyspnea
23	27	80 mgm.	0.14	* 69	+++	—	++	++	—	No dyspnea
24	26	do.	0.14	* 58	+++	—	++	++	—	No dyspnea
25	38	90 mgm.	0.14	* 57	++	—	—	—	—	No dyspnea
26	25	None	0.14	* 67	++	—	—	—	—	Coccidiosis
27	23	do.	0.14	* 69	+++	—	—	—	—	No dyspnea
28	23	do.	0.07	* 38	+	—	—	—	—	No dyspnea

\* Died.

+ Etherized.

The findings in this series of experiments are unique, for so far as we have been able to determine, an acute lethal tuberculosis had not previously been produced in rabbits with the small infecting doses of human type tubercle bacilli here used. Several of the sensitized rabbits after inoculation developed the clinical picture described by Theobald Smith in rabbits inoculated with the bovine type of the organism. Eight of the sensitized animals developed dyspnea, and five died from tuber-

culosis within sixty-seven days after inoculation. In five sensitized and in two control animals, tubercles developed at or near the site of the intravenous inoculation. The significance of this is not clear, inasmuch as, contrary to expectation, the animals in which it developed showed no apparent difference in general reaction from that shown by those in which no local lesion developed. With the exception of two pairs of animals, the tuberculosis which developed was more extensive and more severe in the sensitized rabbits than in the non-sensitized infected controls. Certainly it is evident that in most of the rabbits resistance to moderate sized doses of human type tubercle bacilli—doses smaller than those used by Theobald Smith in his classical experiments—is lowered by sensitizing with our protein. What the effect of hypersensitiveness on infection with very minute doses would be, we have no evidence to show.

The results of the above cited experiments are interesting. They offer material for thought and for the formation of hypotheses. For the present, however, it seems wiser not to theorize but to rest content with a statement of the facts.

In no instance can the diminution of resistance to infection when it occurred be attributed to the treatment of the animals with too large amounts of the protein used, for amounts were never administered in great excess of that required actively to sensitize. Similarly the doses of tubercle bacilli used to infect were quantitatively estimated, were no larger than those ordinarily employed in similar work and the bacilli inoculated were of low virulence. The results of the experiments on rabbits are especially striking, but it is to be definitely asserted that though it was the rule to find more intensive infection in the sensitized animals than in the non-sensitized controls, still the production of a rapidly fatal tuberculosis in rabbits by inoculation of human type bacilli was inconstant, indeed exceptional.

The experiments already detailed show definitely that in animals with preexisting hypersensitiveness to the tuberculo-protein which we have used, there is in the majority a diminished resistance to infection with tubercle bacilli of the human type and that in a large number of cases no alteration of resistance is to be noted. From these facts it seems clear that hypersensitiveness to this protein was not protective against the small amounts of tubercle bacilli injected, but that it was a neutral or even a baneful factor in the immunization of the animals. It would be interesting to see if sensitization with a tuberculo-protein would afford protection against a subsequent infection with single bacilli or with a very few organisms. The observations we have made upon this phase of the problem have led to no conclusions.

From the data to be gathered from the literature and from an analysis of our observations, broad conclusions do not seem justifiable, nor should any positive correlative inferences with the effects of tuberculin be drawn.

Too few accurate investigations on the constitution of the bacillus tuberculosis have been made to warrant the statement that hypersensitiveness to a particular protein extracted from the bacilli will exercise the same influence on subsequent infection as that which a protein prepared from the organisms

by another method might produce. It does not seem entirely improbable that the protein composition of the bacterium in question may be a complex rather than a simple one; that the protein content of the organisms may be a composite content, consisting of more than a single type of protein substance. A small amount of evidence for such a tentative view is furnished by the variability in the sensitizing power of protein obtained by the method we have used when the time of extraction or the temperature at which the extraction proceeds is altered. Again a dose of one commercial tuberculin at times fails to produce any reaction in a tuberculous host, when an equal dose of what purports to be an identical preparation elicits a well-marked response and vice versa.

Further, with reference to the action of tuberculin in man, it seems unwise to draw inferences from these experiments until the identity of the tuberculo-protein in tuberculin and that obtained by aqueous extraction of tubercle bacilli shall have been established. Work upon this problem is now being carried on in this laboratory.

For the present the following conclusion seems justified:

Hypersensitiveness produced in guinea-pigs and in rabbits by sensitization with a protein obtained from the bacillus tuberculosis, human type, by water extraction, exerts a baneful or a neutral influence on a subsequent tuberculous infection. Whether or not a similarly produced condition of hypersensitiveness would influence differently the course of infection with a very few organisms cannot be stated.

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## A CONSIDERATION OF THE MILK SUPPLY OF BALTIMORE.

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In common with other large cities, Baltimore is faced with the important and complicated problem of its milk supply. The rôle which this product plays in nutrition, having served from time immemorial as one of the chief foods of the human race, is unfortunately not the only relation which it occupies towards man. It is also one of the chief agencies in the transmission and spread of disease. Milk may convey to man, for instance, certain infections of the animals producing it such as Malta fever, tuberculosis, foot and mouth disease, and may spread from individual to individual such diseases of man as typhoid fever, diphtheria and tuberculosis. In addition the summer diarrhoeas of children are somehow or other related to an impure milk supply which must assume the responsibility also for such maladies as "septic sore throat" although here it is by no means clear whether the organisms causing the infection are derived from man or animals. As a result of this peculiar relation to us the question of milk becomes at once extremely important. City officials must not only see that this food when delivered to the consumer has a definite nutritive value, they must guarantee, if possible, that it will not produce illness among those who use it, to which end they must insist upon the most rigid regulations to prevent its contamination by bacteria pathogenic for man. It is by no means easy, however, to determine how this can be accomplished and during the past few years we have seen in America most elaborate chemical and bacteriological studies of milk and exhaustive investigations of the conditions under which it is produced. In such cities as Washington, New York, Boston, Philadelphia and Rochester municipal employees, laboratory investigators and private philanthropists have united in the effort to discover the measures which must be adopted in order that milk of a satisfactory character may be

obtained. It is agreed that milk from unhealthy animals, from animals suffering from tuberculosis, particularly tuberculosis of the udder or from inflammatory conditions of the udder must be excluded from sale. Furthermore, milk produced under unhygienic conditions, improperly handled at the dairy farm, during transportation, or by the retailer must also be excluded, not because such milk is in itself an improper food, but because it is more likely to be contaminated by disease-bearing germs. As the most convenient and satisfactory method of determining whether the various avenues are closed by which milk may be polluted, bacteriologists now almost universally depend upon a bacterial count, that is an estimation of the number of aerobic organisms in the milk. Various cities have adopted different standards forbidding the sale of milk containing more than a certain number of organisms. These standards vary from thirty thousand to one million bacteria per cubic centimeter as the highest number of organisms which milk may contain and still be lawfully sold. It must be remembered, however, that the aerobic bacteria which are counted in milk are species which may be regarded as perfectly normal to it, and that they are, at least in most instances, without pathogenic properties. Indeed from the theoretical standpoint it is difficult to understand why milk containing a large number of the organisms indigenous to it is of a different nutritive value or is more likely to convey disease than milk with a small number of germs of the same character. Nevertheless, there is a good deal of clinical evidence for the view that excessive numbers of bacteria in milk may be productive of intestinal disturbances. Aside from theoretic laboratory questions or clinical discussions the estimation of the number of bacteria gives us the best possible information as to the conditions under which the milk is originally obtained at the

dairy farms, and during its transportation, the temperature at which it is kept, and its age. From practical experience in large cities, it may now be regarded as essential in maintaining the health of communities that milk containing an excessive number of bacteria must be excluded from sale or sold under rigid precautions, not merely because of the danger which these bacteria themselves present to man but because they are so likely to be accompanied by the germs of specific disease.

The milk in Baltimore varies greatly in character. On the one hand we have a number of dairies which sell bottled milk of a high degree of purity, the owners and managers of these dairies endeavoring conscientiously to live up to the dictates of modern knowledge in regard to the handling of this product. On the other hand we have large quantities dispensed in small shops and corner groceries under the filthiest conditions, and coming from dairies where no proper measures of cleanliness are carried out. We have thus a marked difference in the quality of the milk used by the rich or well-to-do and by the poorer classes. The complexity of the situation is indicated by the fact that there are over 4000 stores in Baltimore which dispense milk, the majority of these stores supplying it over the counter, the so-called "dipped milk." The amount of bottled milk sold here is increasing, however, and of this amount a considerable proportion is pasteurised, that is, heated to a temperature sufficient to destroy not all but a large number of the organisms present in it. The Baltimore milk supply comes from nearly 2400 farms in Maryland and the milk question is, therefore, a state as well as a city one.

The Department of Health of Baltimore has been grappling with the problem for some years and in their various publications may be found interesting and valuable data in regard to the milk sold here. For some time we have been interested in the question from the laboratory standpoint and on various occasions have made systematic examinations of the milk purchased from the small shops in the vicinity of The Johns Hopkins Hospital. Our results are much the same as those of the city Department of Health. The milk problem must be attacked from various standpoints, however, and by a number of different investigators if good is to be accomplished. I wish to call attention, therefore, to the data obtained in the year 1911 by Dr. de Angulo and in 1912 by Mr. Joseph.

#### REPORT FOR 1911.

BY CARY FINK DE ANGULO, M. D.

During the five months of 1911 from January to June we examined a large number of samples of milk collected in various small shops in Baltimore. The conditions under which this milk was distributed were so unsatisfactory, there was so great an opportunity manifest for contamination by bacteria that it seemed quite impossible to classify the distributing centers in any satisfactory way. Our samples were obtained in part from East Baltimore, but many were collected in the western and southern sections of the city in the poorer districts. They represent the "dipped milk" sold so commonly to the poor people of this city. At no shop visited could the conditions be described as satisfactory. The supply of ice was

usually quite insufficient, much of the milk was kept in open vessels and slovenly attendants were employed to handle it, usually with dirty utensils. Various methods of making bacterial counts were employed at different times but eventually we came to regard gelatin plates kept at room temperature, 48 to 72 hours, as the most reliable. Endo's medium was used on a group of samples with a view to discovering the number of *Bacillus coli* forms present, but the results were in general not so satisfactory as those obtained from a dextrose fermentation tube. The data found in this way proved interesting but the results were not sufficiently constant to indicate a definite relation between the bacterial count and the extent of fermentation. At the same time the Smith tube gives us valuable information about milk and further work may reveal some law by which the extent of fermentation may be used as an index of pollution as in the study of water. From among the many examinations made we have selected 25 which illustrate our results in a general way. The average of the 25 samples was a trifle less than nine million bacteria per cubic centimeter which may be regarded as fairly high considering the fact that the samples were collected in cold or moderate weather. With the exception of No. 3, the first nine samples examined during the winter showed but a relatively small number of bacteria, whereas the samples collected later in the year showed usually a much higher count.

#### MILK EXAMINATIONS IN 1911.

Sample No.	Date	Bacterial Count	Fermentation of Dextrose in Dilution
1	1/21	500,000	1-1000 negative
2	1/30	2,600,000	1-1000 positive
3	2/7	10,000,000	1-10,000 positive
4	2/11	1,300,000	1-1000 negative
5	2/4	3,000,000	1-100 positive
6	2/17	1,300,000	1-10,000 positive
7	3/14	1,800,000	
8	3/16	1,200,000	
9	3/20	1,225,000	
10	3/27	6,200,000	
11	3/28	46,000,000	1-1000 negative
12	3/30	5,200,000	1-1000 positive
13	3/31	35,700,000	1-1000 positive
14	4/1	5,000,000	1-1000 positive
15	4/21	6,780,000	1-1000 positive
16	4/24	11,700,000	
17	4/25	6,200,000	1-1000 positive
18	4/28	5,500,000	1-100 negative
19	4/28	21,000,000	1-100 negative
20	5/5	13,000,000	
21	5/8	4,560,000	1-100 negative
22	5/8	1,400,000	1-100 positive
23	5/15	21,400,000	1-1000 positive
24	5/15	8,900,000	1-1000 positive
25	5/16	12,000,000	1-1000 positive

#### REPORT FOR 1912.

BY MORRIS JOSEPH.

In the spring months of 1912 we were enabled to make a systematic examination of the market milk sold in East Baltimore. The various shops and corner grocers from which milk is distributed were visited personally, careful notes made of the conditions found, a sample of milk obtained and taken to



the laboratory for examination. As a result of the procedure adopted in collecting the specimens it was possible to study but a limited number. The method of examination employed was that which obtains usually in such work. Various dilutions of the milk were made and planted in agar and in fermentation tubes. The plates and tubes were then incubated at 37° C. Agar plates and the body temperature were selected for the work in order to determine whether any correlation exists between the bacterial count and the fermentation reactions, although it is well known that gelatin at room temperature gives higher bacterial counts for milk than agar at 37° C. The various data obtained in this investigation have been arranged in the accompanying chart. A number of interesting points may be mentioned in regard to it. The lowest count, fourteen thousand, was given by a sample of pasteurised milk obtained from a delivery wagon while the highest count, thirty million, was obtained from a dirty shop with poor ice supply, a shop under suspicion and supervision of the Board of Health. There is in general a correlation between the bacterial count and the general conditions of handling the milk. This correlation is by no means exact, however. One can only say that where excessive numbers of bacteria were found in the milk a reason could be seen in the method of handling as in sample No. 7 where over thirteen million bacteria were found on examination and the milk had been kept in an uncovered pitcher, or in sample No. 15 where a count of over seventeen million was obtained from milk sent to Baltimore from Pennsylvania and necessarily long in transit. All the samples of dipped milk which showed a low bacterial count, that is, under one million, as in samples Nos. 1, 2, 6, 12, 16, 18 were from shops where the general conditions, especially as to the ice supply, were excellent, while other specimens in which the bacteria were few in number were either fresh milk as in sample No. 5 or bottled milk as in sample No. 13. Two of the wagon samples, Nos. 11 and 14, showed a low bacterial count while the third sample from a wagon, No. 23, which showed a count of over a million had been insufficiently protected by ice. In 5 cases, samples Nos. 8, 9a, 17, 21 and 24, a high bacterial count is distinctly associated with poor ice supply or careless methods of handling. In other instances such a count is not explained by any conditions observed in handling as in sample No. 25 where over ten million bacteria were found in a cubic centimeter of milk from an excellent shop. It is evident that the conditions under which milk is handled, its protection by ice, its age, all are of definite influence in determining the bacterial content, but that the question is extremely complicated owing to a number of other factors such as the conditions at the dairy farm, the period of time during which the milk is in transit and its refrigeration at this time.

In general there is no definite relation between the bacterial counts and the extent of fermentation. This is not surprising in view of the fact that our counts are made of all varieties of bacteria both fermenters and non-fermenters. The observations on this point, however, are too few in number to give us any exact information.

## MILK EXAMINATIONS IN 1912.

Sam- ple No.	Date	Bacterial count	Fermenta- tion in dex- trose posi- tive and du- ration of	Remarks
1	4/12	226,000	1-1000	Shop clean. Milk carefully handled. Sufficient ice supply.
2	4/12	817,750	1-1000	Shop clean. Milk and utensils carefully handled. Insufficient ice supply.
3	4/15	14,000	1-10	Pasteurised milk from wagon. Wagon clean. Driver neat and careful.
4	4/15	30,222,000	1-100	Shop clean but attendants dirty. Ice supply insufficient on first visit but satisfactory on second visit.
4a	4/22	3,070,000	1-100	This shop was under Board of Health supervision.
Samples Nos. 4 and 4a were from same dairy.				
5	4/19	250,000	1-1000	Shop crowded. Woman in attendance careless and untidy. Ice supply limited. Sample was from fresh milk.
6	4/22	510,500	1-10,000	Shop fairly clean. Milk properly handled. Insufficient ice.
7	4/26	13,768,750	1-10,000	Shop clean. Owner neat. Milk kept in earthen pitcher uncovered. No ice supply.
8	4/26	4,137,750	1-10,000	Shop was in a filthy condition, stuffy and crowded. Owner and wife careless and slovenly. Utensils dirty. Ice insufficient.
9	4/29	1,244,500	1-10,000	Shop small, fairly clean. Milk cans open.
9a	5/3	11,875,000	1-10,000	No ice supply. Girl in attendance clean and careful.
Samples Nos. 9 and 9a were from same shop.				
10	4/29	5,952,250	1-10,000	Shop and attendant very clean. Milk carefully handled.
11	5/6	423,600	1-1000	Wagon sample. Driver and utensils clean. Milk carefully handled.
12	5/6	510,600	1-100,000	Shop and utensils clean. Milk cold and carefully handled.
13	5/10	562,000	1-10,000	Sample of bottled milk from supply used in manufacture of ice cream. Shop clean. Owner careful.
14	5/10	106,250	1-1000 neg.	Sample from wagon. Driver careless. Ice sufficient.
15	5/13	17,720,000	1-1000	Sample of milk sent from Pennsylvania on railroad. Shop and owner clean and neat.
16	5/13	697,500	1-1000 neg.	Shop untidy. Attendant clean. Ice sufficient.
17	5/17	8,700,000	1-1,000,000	Shop and woman in attendance clean. Sufficient ice. Milk carelessly handled.
18	5/17	704,000	1-1000	Shop and attendant clean and neat. Ice supply sufficient.
19	5/20	2,460,000	1-100,000	Shop and attendants neat, clean, and milk carefully handled. Ice protection sufficient.

Sample No.	Date	Bacterial count	Fermentation in dextrose positive in dilution of	Remarks	Sample No.	Date	Bacterial count	Fermentation in dextrose positive in dilution of	Remarks
20	5/20	1,381,500	1-1000	Store and woman in charge clean. Milk carefully handled. Utensils clean. Ice sufficient.	23	5/27	1,243,000	1-1000	sent a remnant of milk left in the can.
21	5/24	21,094,000	1-10,000	Shop and attendants untidy and dirty. Milk carelessly handled. Insufficient ice supply. This shop caters chiefly to negroes.	24	5/27	1,620,000	1-10,000	Wagon sample. Wagon and driver clean. Insufficient ice.
22	5/24	11,227,000	1-1000	Shop and woman in charge clean. Milk carefully handled. Sample repre-	25	5/27	10,210,000	1-100,000	Store and boys in charge clean. Milk protected by ice, but carelessly handled.
									Shop clean. Man in charge neat in appearance. Milk carefully handled and protected by ice.

## MALUM PERFORANS IN DIABETES MELLITUS.

### A REPORT OF SEVEN CASES.

By JOHN T. SAMPLE, M. D., and W. L. GORHAM, M. D.

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*Malum perforans* or *mal perforant* in diabetes mellitus was first described by Marquez<sup>1</sup> in 1866, although it was Puol<sup>2</sup> who, some nine years later, called attention to its not infrequent occurrence in that disease. Since 1875, there have been numerous communications on the subject by various observers [Clement (1881); Kirmisson (1885); Jeannel (1886); Heusner (1885); Laffon (1885-6); Wessinger (1889)]. Naunyn<sup>3</sup> in 1895 reported seven cases in his large series of diabetic cases and Adrian<sup>4</sup> sometime later collected an extensive bibliography.

At the request of Professor Barker we have made a study of the clinical aspects of *mal perforant* as a complication of diabetes mellitus based upon the findings in seven cases admitted to The Johns Hopkins Hospital.

The first and sixth cases of this series were studied by us personally, the details of the others were taken from the hospital records.

CASE 1 (Medical No. 26835).—G. K., æt. 51, white, single, a solicitor, was admitted to the hospital January 18, 1911.

Complaint: "Sores on the feet."

Family History: One sister died of diabetes; otherwise negative and unimportant.

Past History: General health has always been good. He is constipated, as a rule, eats heartily but not of sweets especially. Does not use alcohol or tobacco. Walks a great deal on city pavements.

A little over 10 years ago patient was operated upon in The Johns Hopkins Hospital for a large carbuncle on back of neck. Sugar (2 per cent) was found in the urine at that time, but there were no other symptoms of diabetes. He felt perfectly well and after five days on a restricted diet became sugar-free, and was discharged. Patient admits instructions given about diet were not followed.

He returns to the hospital with ulcers on both feet of seven weeks' duration. The first one appeared on the dorsum of the fifth toe, followed by a larger one on the dorsum of the left foot, and later by one on the external malleolus. They grew progressively worse and pus was discharged. Soon after this an ulcer appeared on the plantar surface of the right foot. About five weeks before admission he was compelled to stop work, because he could not walk. Patient has had no other symptoms. No bulimia, polydipsia, polyuria, nycturia, pruritus, cataract, skin infections or loss of weight.

Physical Examination: Patient is of moderate frame, rather obese; skin pasty, conjunctivæ pale, hearing impaired. Teeth in bad condition, many absent, gums slightly retracted. Scar of old carbuncle on neck. There is slight general glandular enlargement. Thorax is barrel-shaped. Heart and lungs are normal. Pulse slow, regular, low tension, radials moderately thickened. Abdomen negative. There is no trophic disturbance of fingers. Deep reflexes of arms are present. No edema of ankles. Considerable pigmentation and many irregular scars on shins. The reflexes are present and normal.

Right Foot: Fairly good pulse in the dorsalis pedis and posterior tibial arteries although both vessels are sclerotic. Over the metatarsal phalangeal joint of first toe is a scabbed area surrounded by desquamation and on plantar surface just back of balls of toes there is a large bluish desquamating area.

Left Foot: Good palpable pulse in both dorsalis pedis and posterior tibial artery. On the dorsum of foot on either side of ankle are small reddish areas capped with scabs surrounded by desquamation. On the dorsum of the big toe is a discharging sinus filled with creamy pus. At the base of the sinus, made up of coarse granulations, a probe can be passed a quarter of an inch forward toward the nail and fully an inch backward toward the ankle. Both sinuses are superficial and do not come in contact with bone. The fifth toe is swollen and shows a similar sinus on its dorsum, discharging pus. Sense of touch is well preserved over both feet except over the fifth toe of the left foot. Plantar response normal.

X-ray negatives show no bony involvement.

Blood Examination: Red blood cells 5,000,000; white blood cells 8000; hæmoglobin 90 per cent (Sahl).

Urine: Quantity 2000 cc., 24-hour specimen; sp. gr. 1040, yellow, clear, acid, trace of albumin, 4 per cent sugar, 80 gms. per liter; no red or white corpuscles, no casts, no acetone, no diacetic acid.

Wassermann Reaction: Negative.

Ophthalmoscopic Examination: Normal fundi, no marked arterial sclerosis.

Course: Patient's tolerance for carbohydrates was found to be 60 gms. of white bread. On the eighth day he became sugar-free with a loss of six pounds in weight. At no time did acetone bodies appear in the urine. The specific gravity of the urine fell to 1030 and the total amount to 1500 cc.

In the local condition of feet there was a noticeable improvement at first as a result of rest, elevation, warm cloths, washing with peroxide and dressing with balsam of Peru.

February 12. The ulcer on the surface of the fifth toe, left foot, is healing well with rich red granulations; the one on the

dorsum has changed very little and has still a punched-out appearance.

February 19. There is a wide area of softening about the sinus on the dorsum of the left foot. Deep probing and pressure brought out about a drachm of pus. The surgical opinion is that free incision and drainage would favor healing. The ulcer on the fifth toe, left foot, is practically filled with healthy granulation tissue.

Patient left in March before his feet were entirely healed and was not heard of again until three months later. He had restricted his diet, dressed his feet carefully and rested. The ulcers were entirely healed and patient is walking about the streets daily. A 24-hour specimen of urine measured 1700 cc. and contained 2 per cent sugar and a trace of albumin, no casts, no acetone, and no diacetic acid. Three months later patient again reported. He was in good condition and working daily as a solicitor.

CASE 2 (Medical No. 22710 and 24239).—A. F., æt. 48, female, white, housewife, was admitted to the hospital June 1, 1908.

Complaint: Abdominal pain, ulcer on left foot and malaise.

Family History: No history of diabetes. A history of tuberculosis in family. Negative for rheumatism, neoplasm, or nervous affections.

Past History: General health has been fair. Patient has always been constipated. Menstruation stopped at age of 43. Has had pelvic inflammatory disease. Seven years ago her physician told her she had diabetes. She was then suffering from dimness of vision, increased hunger and thirst, polyuria, pruritus and eczema of the genitalia. Since then, patient has been in rather poor health.

Physical Examination: There is a cataract in left eye. Chest: Practically normal. Heart: Negative. Abdomen: Some tenderness in the right inguinal fossa and a palpable right kidney. Extremities: Reflexes in arms normal. Knee jerks are not obtained. Sensation over feet and ankles showed no marked disturbance. The amount of arteriosclerosis was only moderate. The left dorsalis pedis gave good pulsation, but none was obtained in the posterior tibial. Arteries on right side normal. There was no alcoholic history and no special mechanical factors, such as long hours on feet or tight shoes, played a part.

On the ball of the left great toe is an ulcer 0.5 cm. in diameter with a purulent discharge, surrounded by an indurated area. Over the dorsum of the right foot is a patch of erythema but no loss of epithelium. Scars of healed ulcers are present on ball of the right and left great toe. Area of fluctuation on dorsum of the right great toe, incised, and a bloody purulent discharge obtained. On June 3 urine showed 5 per cent sugar. Patient was made sugar-free after two days of carbohydrate-free diet. No acetone or diacetic acid appeared. By September, 1909, the patient had gained 24 lbs. and left hospital much improved, with feet healing satisfactorily.

In April, 1910, new sores on the legs and a discharging ulcer on the ball of the left great toe were noted. Patient had lost weight and had aggravation of previous symptoms. Examination showed a deep punched-out ulcer with induration and partial scab formation on the left thigh below ilium. On the right little toe and extending up the dorsum of the foot was the remains of a large bleb or bulla, the outer portion being covered with a cheesy scab. The end of the second toe showed a similar lesion.

Blood Examination: Red blood cells 4,224,000; white blood cells 10,000; hæmoglobin 82 per cent (Sahli).

Wassermann Reaction: Negative.

Patient's carbohydrate tolerance was found to be 80 gms. of white bread and complete healing of ulcers followed regulation of diet and rest.

CASE 3 (Medical No. 6916).—J. H., white, male, farmer, æt. 56, came to hospital December 11, 1896.

Complaint: Pain in stomach and swelling of ankles.

Family History: Negative for diabetes, tuberculosis, rheumatism or neoplasm.

Past History: Has been in good health most of the time, but for the last six years he has had diabetes to his own knowledge. During this period he has given more or less careful attention to his diet and been at work and fairly well, up to the last six weeks, when he began having pain in stomach, diarrhoea and swelling of legs and face.

On physical examination, enlarged heart and moderately increased blood pressure and œdema were noted. Urine showed sugar and trace of albumin. He was rendered sugar-free on a carbohydrate-free diet, but 2 to 5 per cent of sugar appeared when carbohydrates were added to his food. On January 3 a blister was noted on the left foot at the base of the great toe after rest in bed for twenty-three days. This developed into an ulcer 3 cm. in diameter with an angry-looking base. The reflexes were not obtained at either patella. There was some sclerosis of veins and the arterial walls were thicker than normal. Sensation was not tested.

Patient had a history of very moderate use of alcohol. One drink of whiskey a day.

There was apparently no mechanical factor concerned.

The ulcer gradually healed, but three months later gangrene of both feet developed. Patient had a marked chronic nephritis in addition to his diabetes and he died in April.

CASE 4 (Medical No. 16504).—R. N., white, male, æt. 65, clerk, was admitted to the hospital November 23, 1903.

Complaint: Ulcer on toe.

Family History: Negative for diabetes, tuberculosis, neoplasm or rheumatism.

Past History: General health had always been good. No trouble from headaches, no eye, ear, nose or throat symptoms.

Cardio-respiratory and gastro-intestinal symptoms: Negative. Normal appetite. Has always drunk large amounts of water. No history of polyuria, no pruritus. Nervous symptoms: Negative.

Habits: Fairly regular. No alcoholic excess. Patient is on his feet a good deal and troubled with corns. Wears rather tight shoes.

Present trouble began about nine months ago with a corn on his right great toe which failed to improve. He finally cut and scraped it, but instead of healing, a deep ulcer developed and has persisted ever since. About five months ago 4 per cent sugar was found in his urine. From then until present time he has been on a diet and only a trace of sugar has been found since.

On physical examination the head, heart and lungs showed nothing abnormal. Abdomen was also negative. Extremities: Upper were negative, knee jerks were not elicited upon reinforcement. Sensation not tested. There was no special arteriosclerosis of the vessels of the feet. On the lower surface of the right great toe was an ulcer about 1 cm. in diameter, with a slight area of induration and very little discharge. On regular ward diet only 0.2 per cent of sugar was found. Patient remained in the hospital only a week and some slight improvement of ulcer was noted.

CASE 5 (Medical No. 16634).—White, male, æt. 48, a merchant, was admitted to hospital on February 5, 1909.

Complaint: Ulcers on feet, loss of weight.

Family History: One brother had diabetes. No history of tuberculosis, neoplasm or rheumatism.

Past History: Up to a year or so ago patient had been in good general health. Head gave him no trouble. No trouble with eyes, ears, nose or throat. Heart and lungs gave no symptoms. Bowels regular, normal appetite, no excessive thirst or hunger. He has had no polyuria or pruritus. No nervous symptoms. About a year ago ulcers appeared on the sole of the left foot which were



aggravated by walking. They first appeared as blisters on the ball of the large toe and over the fifth metatarsal phalangeal joint. Last spring sugar was discovered in the urine and the patient has lost over fifty pounds up to time of admission. Patient has always been fond of sweets, but has had no abnormal appetite, thirst or polyuria. No alcoholic excess.

Physical Examination: Undernourished, shows signs of loss of weight. Head negative. Chest and abdomen show nothing noteworthy. Extremities: Upper are normal with slightly increased reflexes, lower show exaggerated patellar reflexes. No apparent disturbance of sensation about ankles or dorsum of feet. There is a moderate thickening of arteries. Patient was accustomed to take long walks and shoes caused some rubbing. At present there is a healed ulcer on left foot. On right are partially healed ulcers at base of great toe and over fifth metatarsal phalangeal joint. These areas are not sensitive to pressure. The skin of toes has been shed with the nails and new skin has formed beneath. With restricted diet patient was made sugar-free and ulcer had healed when he was discharged.

CASE 6 (Medical No. 26022).—M. L., white, female, æt. 57, housewife, entered hospital August 10, 1910.

Complaint: Sugar in urine and ulcer on left foot.

Family History: Negative for diabetes, rheumatism, neoplasm or tuberculosis.

Past History: The patient was practically well up to three years ago when symptoms of present illness began. No trouble with head; no cardio-respiratory difficulty, digestion has been good and bowels only slightly constipated. There has been no trouble relative to genito-urinary system. Some slight nervousness but nothing outspoken. Habits have been good with no history of alcoholic excess. Patient is on her feet only about the average amount. She admits wearing tight shoes.

Present illness began three years ago with polydipsia, polyuria, pruritis vulvæ, double vision and attacks of hemianopia. Accompanying these symptoms discoloration of certain small areas at points of pressure from shoes appeared on both feet. These spots would partially clear up and again reappear as general symptoms varied. Sugar was found in the urine and for the last six years a fairly strict diet was used for short periods, with improvement while it was maintained. For several months, about a year before admission, patient says that she had a small superficial ulcer on the right great toe which healed rapidly as her general condition responded to a careful dietary. The present ulcer on the left great toe has existed for six or seven months, and recently there has been a sero-purulent discharge from it, but it gives no pain.

On examination the patient was found to be undernourished; pallor striking. The head was practically negative. Eye grounds showed no evidence of hæmorrhage or exudate. No diabetic retinitis. There was nothing abnormal made out in chest or in abdomen. Extremities: Arms showed no weakness and reflexes were present. The reflexes of legs were present but rather sluggish. The sensation over the legs and dorsum of the feet was intact. The blood vessels showed moderate thickening. The dorsalis pedis and posterior tibial arteries pulsed in both feet. On the left foot at point of pressure under the ball of the great toe is a large punched-out ulcer with clean, moist base, precipitous edges and some induration. No pain was caused in probing the ulcer. No sinus was found, but a purulent discharge welled up on pressure. The ulcer was dressed with usual local applications daily but healing did not progress at all satisfactorily. The carbohydrate tolerance was determined to be 40 gms. of white bread. Urine 1000 to 2000 cc. daily, no acetone or diacetic acid appeared. X-ray examination revealed a chronic osteomyelitis of the first left metatarsal bone and the toe was amputated. Recovery was rapid.

CASE 7 (Medical No. 26411).—A. C., colored female, æt. 60, housewife, admitted to hospital October 21, 1910.

Complaint: Loss of weight and a sore spot on heel.

Family History: No diabetes, no tuberculosis, no neoplasm, no rheumatism.

Past History: Unimportant up to two years ago when symptoms of the present trouble began, with loss of weight and easy exhaustion. She kept about her work but has steadily grown worse. Two weeks before admission she began having excessive thirst and took a small amount of whiskey each day. She noticed frequent micturition and the passage of large amounts of urine at each voiding. Her right leg became numb and tingled and a sore spot appeared on the right heel.

Examination: Physical unimportant except for the lower right extremity. The leg showed some hyperæsthesia especially about the heel. There was some sclerosis of arteries and the dorsalis pedis and posterior tibial were felt with difficulty. The patellar reflexes were absent.

The right heel shows a small hæmorrhagic area covered by thin unbroken skin. There is very little induration to be made out. The carbohydrate tolerance was found to be high—200 gms. of white bread, and no diacetic acid or acetone appeared. When patient was discharged there was still some redness about heel, but the pain and tenderness had left.

The exact etiology of *malum perforans* is still undetermined, although one does not have to look far for theoretical explanations. Several authors believe the ulcer depends upon changes in the peripheral nerves. Against this view, however, is the fact that the sensory disturbances are slight; further, the ulcers do not present the same picture as that seen in known forms of chronic neuritis. There is not, in the literature, a well-authenticated case of diabetic *mal perforant* due to neuritis. Neural change may be secondary rather than primary. The mechanical factor is apparently of some etiologic importance and has its supporters. This mechanical theory holds that the ulcer is due to the constant pressure exerted on certain parts of the feet in walking or standing. In favor of the theory is the marked improvement which, in some cases, follows upon rest in bed and removal of pressure. Against this theory is the stubborn refusal of some ulcers to heal in spite of the best local treatment. It would seem that the mechanical factor can not be more than a contributory cause. A third theory offers vascular change as the primary cause of perforating ulcer. In a majority of the cases no arteriosclerosis, or only a slight grade, exists in the vessels leading to the part affected. Endarteritis obliterans must be borne in mind. It, however, develops secondarily in the course of *mal perforant* and may be absent in some cases altogether. Vascular change, therefore, like pressure, may be a contributory factor but will not, alone, explain the lesion. The view that the true cause lies in a disturbance of tissue vitality due to the existing hyperglycæmia seems a rational one. As a result of this lessened tissue resistance one might well explain the frequent appearance of furuncles, carbuncles and gangrene; as a rule, improvement of glycosuria and ulcer are coincident.

The approximate frequency of the occurrence of *mal perforant* in diabetes may be judged from the following: Naunyn reported 7 in 100 cases, Williamson<sup>5</sup> 4 in 140 cases, and at The Johns Hopkins Hospital there have been 7 in 275 cases. Fitz and Joslin<sup>6</sup> report that at the Massachusetts General Hospital from the year 1824 to 1898 there were admitted to the wards 172 diabetics; only one case of round ulcer is recorded, and this improved under treatment. Among 687

diabetics, therefore, there were 19 with perforating ulcers, or 2.7 per cent. Gascuel,<sup>7</sup> 1890, found among 91 cases of *mal perforant* of all types 14 cases of diabetes, i. e., 15 per cent.

Perforating ulcer occurs in the male vastly more often than in the female. Men are of course more exposed to trauma and to chronic irritation of the feet. Alcohol is used to a greater extent by men, but it has not been shown to have any definite causal influence.

Nearly every case recorded in the literature has occurred in an individual over forty years of age. It is a malady, therefore, of middle, or of late life.

The glycosuria in these cases is almost always of a mild grade. Scarcely an instance of severe glycosuria with *mal perforant* is to be found in the literature. Naunyn cites a possible exception in the patient described by Buzzard<sup>8</sup> in whom there was 4 to 5 per cent of sugar in the urine on a slightly restricted diet; still the total amount of urine voided in the twenty-four hours was not over two liters. The mild nature of the diabetes may be in part dependent upon the fact that perforating ulcer occurs in elderly people. All of Naunyn's 7 cases, save one, were over forty; all 4 of Williamson's cases were over fifty; and all 7 of our cases were over forty-five years of age.

The *mal perforant* of diabetes resembles very closely in appearance that of tabes, but is to be distinguished from it, and from other forms of ulcer, by the location of the lesion. According to Naunyn, and from our own case reports, the diabetic perforating ulcer occurs more often than not at an "atypical" place. In one of Naunyn's cases (No. 79, p. 268) the ulcers were on the right index and little fingers; in another (No. 81, p. 271) the ulcer was on the lateral side of the foot, just under the external malleolus. In our cases, similar examples are to be found (see case reports).

The initial lesion is often in the form of a small vesicle which later develops into an ulcer, or the process may take its origin from an infected corn. The condition may be superficial, limited to the shin and subcutaneous tissues, or it may extend more deeply, involving bone or cartilage, or opening into a joint. The metatarsal phalangeal joint is a favorite seat for such a pathological change. The superficial ulcer tends to heal in a short time when submitted to the proper treatment (Cases 1 and 2 of our series) while the ulcer of the deep, burrowing type is prone to last for a considerable period (Case 6). Sequestra are rarely expelled. There should be no confusion, as a rule, between perforating ulcer and the progressive ulcerations of diabetic gangrene. The former rarely, if ever, spreads out upon the surface, which is in sharp contrast with the behavior in gangrene. However, confusion does sometimes arise, and there are also cases in which perforating ulcer is associated with a deep seated phlegmonous inflammation and gangrene. Naunyn believes that febrile manifestations in *mal perforant* speak for an associated infectious process arising in the ulcer.

Anesthesia of the ulcer and its surrounding tissue may occur in diabetic *mal perforant*, but it is no more constantly seen than in non-diabetic cases. We have not found it outspoken in any of our cases.

The knee jerks apparently differ in individual cases. Wil-

liamson found them absent bilaterally in two of his 4 cases, and absent on one side in a third case. In our series of 7 cases the knee kicks were absent in 4, and present in 3 cases.

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#### NOTES AND NEWS.

Dr. Frank O. Beall is Associate Professor of Surgery, Texas Christian University, Fort Worth, Texas.

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Dr. Malvern B. Clopton has been appointed Associate Surgeon to the Children's Hospital, St. Louis, Mo.

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Dr. Paul G. Woolley is Director of the Laboratories of the Cincinnati Hospital and Dean of the Faculty of Medicine, Ohio Miami Medical College.

Professor Ludwig Aschoff, of the University of Freiberg in Breslau, Germany, has accepted an invitation to deliver the Cartwright lectures of the Alumni Association of the College of Physicians and Surgeons, New York, between March 15 and 20, 1913. The exact date and subjects of the lectures will be announced later.

The American Surgical Association has appointed a committee consisting of Drs. William L. Estes, South Bethlehem, Pa.; Thomas W. Huntington, San Francisco, California; John B. Walker, New York City; Edward Martin, Philadelphia; and John B. Roberts, chairman, 313 S. 17th Street, Philadelphia, to report on the operative and non-operative treatment of closed and open fractures of the long bones and the value of radiography in the study of these injuries. Surgeons, who have published papers relating to this subject within the last ten years, will confer a favor by sending two reprints to the chairman of the committee. If no reprints are available, the titles and places of their publication are desired.

JOHN B. ROBERTS, *Chairman*.  
313 S. 17th St., Philadelphia, Pa.

### NEW PUBLICATIONS.

The individual papers which make up the volumes of The Johns Hopkins Hospital Reports will in future also be published as Monographs and put on sale by The Johns Hopkins Press. The first three, to appear shortly, are:

Free Thrombi and Ball Thrombi in the Heart. By J. H. Hewitt, M.D.

Primary Carcinoma of the Liver. By M. C. Winternitz, M.D.

Benzol as a Leucotoxin. By Laurence Selling, M.D.

### ARMY MEDICAL CORPS EXAMINATIONS.

The Surgeon General of the Army announces that preliminary examinations for the appointment of First Lieutenants in the Army Medical Corps will be held on January 20, 1913, at points to be hereafter designated.

Full information concerning these examinations can be procured upon application to the "Surgeon General, U. S. Army, Washington, D. C." The essential requirements to securing an invitation are that the applicant shall be a citizen of the United States, shall be between 22 and 30 years of age, a graduate of a medical school legally authorized to confer the degree of Doctor of Medicine, shall be of good moral character and habits, and shall have had at least one year's hospital training as an interne, after graduation. The examinations will be held simultaneously throughout the country at points where boards can be convened. Due consideration will be given to localities from which applications are received, in order to lessen the traveling expenses of applicants as much as possible.

The examination in subjects of general education (mathematics, geography, history, general literature and Latin) may be omitted in the case of applicants holding diplomas from reputable literary or scientific colleges, normal schools or high schools, or graduates of medical schools which require an entrance examination satisfactory to the faculty of the Army Medical School.

In order to perfect all necessary arrangements for the examination, applications must be completed and in possession of the Adjutant General at least three weeks before the date of examination. Early attention is therefore enjoined upon all intending applicants. There are at present thirty-five vacancies in the Medical Corps of the Army.





# BULLETIN

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## LECTURES ON THE HERTER FOUNDATION.<sup>1</sup>

By GEORGE H. F. NUTTALL, M. D., PH. D., SC. D., F. R. S.

Formerly Associate in Hygiene, Johns Hopkins University, Fellow of Magdalene College,  
Quick Professor of Biology in the University of Cambridge.

### LECTURE I.

#### SPIROCHAETOSIS.

Under the term "Spirochaetosis" are included those diseases of man and animals due to the spiral microorganisms known as spirochaetes. I shall confine myself to those which produce blood infection—the relapsing fevers—in which a remarkable periodic increase and decrease in the number of the spirochaetes is observable corresponding to alternating rises and falls of the host's body-temperature. Authority is divided as to whether the spirochaetes are protozoa or bacteria, and the matter is a fruitful theme of discussion upon which I shall not enter here. Judged, however, from their pathological effects and their prompt reactions to immune sera and certain drugs, they show a pronounced affinity to protozoa and exhibit phenomena not hitherto observed in bacteria.

As in trypanosomiasis, spirochaetosis is readily induced by inoculation with infected blood, and may thus be communicated almost indefinitely from animal to animal. In one series, for instance, I transmitted *S. duttoni*, with apparently undiminished virulence, through one hundred mice. Again, as in trypanosomiasis (*T. lewisi*, *T. evansi*), infection may take place by feeding.

#### TRANSMISSION OF SPIROCHAETES BY ARTHROPODS.

Investigations conducted during the last few years have demonstrated conclusively that the blood-inhabiting spirochaetes are, in a number of instances, transmitted by blood-sucking arthropods, and I propose to deal chiefly with these results since they are of great practical importance to preventive medicine.

#### SPIROCHAETOSIS IN BIRDS.

In the year 1891, Sacharoff, in the Transcaucasus, demonstrated that a spirochaete, called by him *Spirochaeta anserina*, was the cause of a very fatal epidemic disease in geese. The spirochaetes appeared in the birds' blood shortly before the onset of symptoms, multiplied enormously, and disappeared at the approach of death. He transmitted the disease to geese and fowls by inoculation. In the year 1903, Marchoux and Salimbeni, working in Brazil, observed a similar disease in fowls, and since that date fowl spirochaetosis has been recorded from many parts of the world, the causative agent being now generally known as *Spirochaeta gallinarum*. We know to-day that spirochaetosis in fowls occurs in South-eastern Europe, in Asia, Africa, South America and Australia, and, in all places where the disease exists, is found what Marchoux and Salimbeni were the first to show to be the carrier, the tick, *Argas persicus* (Fig. 1). I have seen blood-films and determined the tick from many different places

<sup>1</sup> Delivered in the Medical Department of The Johns Hopkins University, October 8, 9, and 10, 1912.

where the disease has been recorded. Personally, there is no longer any doubt in my mind as to the identity of *S. anserina* Sacharoff and *S. gallinarum*. *Argas persicus* has accompanied the fowl in its distribution in many parts of the world, but the fowl has got rid of the pest in colder climates as the tick is unable to develop at low temperatures.

Spirochaetosis in fowls is a very fatal febrile disease; the mortality in a yard may attain 40-100 per cent. The disease begins with diarrhoea, followed by loss of appetite and somnolence. The birds' feathers appear ruffled, the comb pale, the birds cease to perch, and, as the disease advances, they lie prostrate upon the ground. Death may take place suddenly during a convulsive attack. The disease occurs at times in a chronic form, the emaciated birds developing paralytic symptoms after apparent recovery. Death takes place in anywhere from 3 to 15 or more days, according to the type of the disease, the body-temperature at the time of death being frequently subnormal. Whereas, in chronic cases,

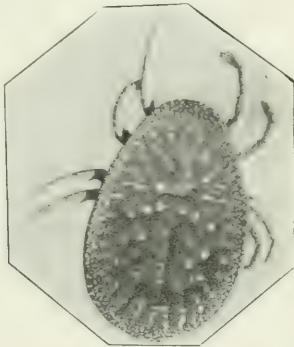


FIG. 1.—*Argas persicus* ;.

the liver and spleen appear atrophied, these organs are much enlarged in acute cases, the liver showing fatty degeneration and at times focal necroses. The fowl spirochaete from Brazil kills geese in 5 to 6 days after inoculation, and produces a fatal infection in ducks, guinea-fowls, turtle-doves, and other birds.

Thanks to the kindness of Dr. Marchoux, I was able, at an early date, to confirm his and Salimbeni's results with infected *Argas persicus* (= *miniatus*) which he sent me from Brazil. Since that date Marchoux, Borrel, and others, also Hindle, in my laboratory, have materially advanced our knowledge of the mechanism whereby the tick infects the fowl. Without wearying you with the details of each experimenter's work, I may summarize it as follows:

The ticks are best rendered infective if they are maintained at a temperature of 30-35° C. after they have fed upon blood containing the spirochaete. If kept at a low temperature, 15-18° C., the spirochaetes disappear very soon from their alimentary tract, and the ticks may bite birds repeatedly without infecting them. They may, however, be rendered infective after three months if placed at 30-35° C.; the spirochaetes

then reappear in their coelomic cavity, as may be shown by cutting off one of the tick's legs and examining the coelomic fluid which exudes from it upon a slide.

When the spirochaetes first enter the tick they soon disappear from the gut, a certain number degenerate, whilst others



FIG. 2.—*Argas persicus*. Section of uninfected tick's Malpighian tubule. (E. Hindle.)

traverse the gut wall and enter the coelomic cavity to circulate all over the body. A number of them die in this situation as evidenced by the frequent presence in the coelomic fluid of pale, scarcely visible, non-motile spirochaetes which are difficult to stain. The spirochaetes next enter the various

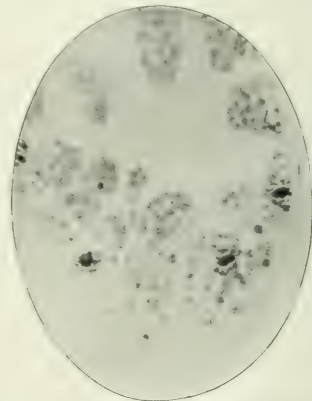


FIG. 3.—*Argas persicus*. Section of heavily infected Malpighian tubule. The cells are filled with agglomerations of coccoid bodies. (*Spirochaeta gallinarum*.)

organs, especially the cells of the Malpighian tubules and sexual organs, in which they break up into a large number of small particles, or coccoid bodies, which multiply by fission and give rise to large agglomerations which can be seen very distinctly in stained specimens (Heidenhain stain).<sup>2</sup> The

<sup>2</sup> Compare Figs. 2 and 3.

coccoid bodies may also be found within the lumen of the gut and Malpighian tubules and in the excreta. In the act of feeding, the tick occasionally voids excrement and exudes a few drops of secretion from coxal glands situated in the first inter-coxal space, the fluid pouring out of a wide duct and being rapidly secreted from the freshly imbibed blood serum. This fluid, as well as the salivary and intestinal secretion of *Argas*, contains an anticoagulin, as I showed with Strickland.

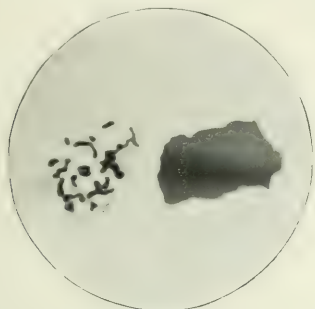


FIG. 4.—*Argas persicus*. Smear of infected ovum of the tick incubated 24 hrs. at 37° C. Coccoid bodies, in a Malpighian cell, developing into spirochaetes. (E. Hindle & B. G. Clarke phot.)

The coxal fluid dilutes the escaped excrement and facilitates its getting into the wound inflicted by the tick. This is doubtless the usual mode of infection, the coccoid bodies in the excrement gaining access to the blood of the host and afterwards developing into spirochaetes, though the latter development has not actually been followed. Marchoux and Couvy (1912) state that infection may, however, take place without coxal secretion being voided. The bird begins to show

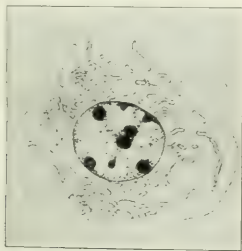


FIG. 5.—*Argas persicus*. Drawing of Malpighian tube cell of embryonic tick maintained 5 days at 37° C. showing coccoid bodies (*S. gallinarum*) developing from spirochaetes. (E. Hindle, 1911.)

symptoms after a period of incubation of about four days following upon the bite of the infected tick.

Although it was denied that the spirochaete of the fowl is transmitted hereditarily to the offspring of *A. persicus*, I expressed the opinion some years ago<sup>3</sup> that there was every probability that it would be found to be transmitted hereditarily as is *S. duttoni* in *Ornithodoros moubata*. Hindle has recently confirmed this supposition (Figs. 4 and 5). Coccoid

bodies are found within the Malpighian cells of the embryonic tick, as described by Leishman for *S. duttoni* in *O. moubata*. If the eggs are maintained at 37° C., the coccoid bodies grow out and assume a form which suggests they are on the way to forming spirochaetes. The spirochaete stage occurs in the coelomic fluid of the tick, but not within its body cells. I may add here that *Argas reflexus* has been shown by Shellack (1908) to transmit the fowl spirochaete.

#### HUMAN RELATIONS IN TROPICAL AFRICA.

Although David Livingstone (1857) was the first to report upon pathogenic effects following upon the bite of the tick we know to-day as *Ornithodoros moubata* (Fig. 6), it was not until the year 1905 that Dutton and Todd, in the Congo, and shortly afterwards, Robert Koch, in German East Africa, demonstrated that this tick transmitted spirochaetosis to man. The British authors made the important observation that the *Spirochaeta duttoni* is transmitted hereditarily to the offspring of the tick, a fact confirmed by Koch, who discovered that 5-15 per cent, and at times 50 per cent, of the ticks harboured the parasite. Koch captured the ticks at resting



FIG. 6.—*Ornithodoros moubata* ♀.

places along caravan routes and in places outside the regular routes. Apparently, owing to German East Africa having been opened to trade for a much longer period than the Congo, the tick appears to be much more widely distributed in East Africa than in the Congo. Dutton and Todd state that in the Congo it only occurs along routes of travel. I have examined a large number of specimens of this tick from various parts of Africa and would note that its geographical distribution is far wider than our present records show for the distribution of relapsing fever in man. There is every reason to fear, therefore, that an extension of the disease will follow with time, unless the natives learn even better than they do to shun the "tampam." In fact, I have an interesting observation to note in this connection which bears out my contention. It emanates from the Rev. John Roscoe, of Cambridge, who gave me the information last year. This gentleman was a missionary in Uganda, where he lived for many years at Kampala in a native-built house having reed walls supported by the usual wooden pillars. To quote his words: "Some of the pillars were in rooms, not in the walls, and it was at the bases of two of these pillars in the room used as a dining room that I noticed the ticks in the year 1896 or about that time. For several years I continued to live in the same house and suffered no harm from them. In more recent years, that

<sup>3</sup> Harben Lectures, 1908.



is, about 1903 or 1904, both Europeans and natives have suffered from "Tick Fever" (*Spirillum*) in houses which were built on either side of the site on which my old house stood. It has been affirmed that the ticks in these houses are the cause of the fever; I can only conclude that in previous years they were innocuous and that they have become nocuous since 1896." I do not know of any similar observation having as yet been recorded.

The disease has repeatedly been transmitted to experimental animals, rats, mice, and monkeys, by means of infected ticks, and in a number of cases unwittingly to experimenters in European laboratories. I may, in this connection, instance the case of Mr. Merriman, in my laboratory, who suffered from the disease in consequence of being bitten by two *O. moubata* (first-stage nymphs) whose biology he was studying. He did not know he had been bitten by the ticks until after two days when he showed me two characteristic bites upon his forearm. His attack followed 16 days after the bites were inflicted, the incubation period being four to six days longer than is usual.

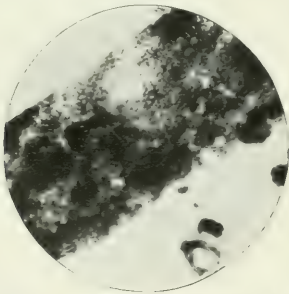


FIG. 7.—*Ornithodoros moubata*. Malpighian tube of 2d stage nymph infected hereditarily with *Spirochaeta duttoni*. A vast number of coccoid bodies fill the malpighian cells. (Sir Wm. Leishman.)

Of 25 monkeys with which Möllers experimented in Berlin no less than 20 died of spirochaetosis. There is, therefore, no possible doubt about the tick being the carrier of the disease.

Möllers' observations were of fundamental importance in relation to the etiology of the disease. He proved that ticks continue to harbour the parasite even after repeated feeds upon clean animals: thus 10 out of 12 monkeys were infected in succession by one lot of ticks which were fed upon them. His stock of ticks had died down to a low point toward the end of the series or the positive results would doubtless have continued longer. A tick may remain infective for 18 months or more after its initial infective meal of blood. He proved, moreover, that the parasites in the tick were transmitted hereditarily to the third generation when the ticks were fed throughout upon clean animals. Another observation possessing considerable interest is that of Manteufel (1910) that the ticks apparently acquire immunity to spirochaetal infection. Hindle has since found that about 30 per cent of the *moubata* sent

to me from Uganda failed to become infected. It is conceivable that the stage of the disease or of the spirochaete's development at which the tick imbibes the parasites may have some influence upon the number of ticks which become infected, as noted by Miss Muriel Robertson for *Trypanosoma gambiense* in *Glossina palpalis*, to which reference will be made in the next lecture. Such a condition might well account for some of the immunity which is stated to occur. We know that there are marked variations in the viability of spirochaetes in relapsing fever blood preserved in vitro. Thus, Novy and Knapp (1906) found that *S. recurrentis* (American strain) survived for 30 to 40 days in defibrinated blood drawn from a rat during the onset of the disease, whereas they only survived 24 hours in blood drawn during the decline.

Although Dutton and Todd, Balfour, and others observed the breaking up of spirochaetes into minute granules in the body of ticks, Leishman was the first to follow the process more clearly. He proved that the coxal secretion was anticoagulant and non-infective, and that the excreta were infective by inoculating them into animals. He found that only

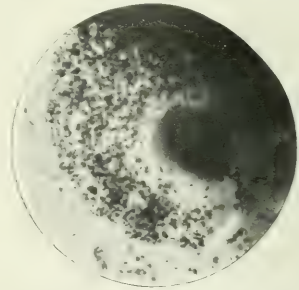


FIG. 8.—*Ornithodoros moubata*. Egg protruding from edge of ovary of infected female and heavily charged with coccoid bodies  $\times 1500$ . (Sir Wm. Leishman.)

when *moubata* voided excreta in the act of biting that animals under experiment became infected. He therefore concluded that the mode of infection is contaminative through the tick's excreta, and not active through its proboscis. Experiments which I carried out, and which were extended and reported upon by Hindle in my laboratory, completely confirm the results of Leishman. If the internal organs of an infected *moubata* are carefully dissected out and well washed in sterile salt solution, it is found that the gut, together with its contents, the Malpighian tubes, the sexual organs and excrement are infective when emulsified and injected into a susceptible animal. The coxal secretion always, and the salivary glands in most cases, give negative results. The few positive results with salivary gland inoculations may well be referred to experimental error in that the glands, in the process of dissection, may easily become contaminated by spirochaetes derived from other organs and be imperfectly cleansed in the process of washing. Inoculations with emulsified eggs of *moubata* have also given positive results as might be expected for spirochaetes have been found in them by a number of

authors. Koch (1905) and Carter (1907) being among the first to demonstrate their presence microscopically in this situation.

After being ingested by the tick, the spirochaetes usually disappear from the lumen of the gut in about nine to ten days, but they reappear if the tick is placed at 35° C. They are then found in the coelomic fluid and their subsequent behaviour is similar to that described in the fowl spirochaete (Figs. 7 and 8).

It is highly probable that other species of *Ornithodoros* play a like part in the etiology of relapsing fever in other parts of the world than those in which *moubata* occurs, the latter being a purely African species. *Ornithodoros savignyi*, which is indistinguishable from *moubata* at a casual glance, and which also occurs in Africa, at Aden, and in India, has been found by Brumpt to convey a spirochaete derived from cases of human relapsing fever occurring in Abyssinia. *Ornithodoros turicata* is suspected in connection with relapsing fever in Colombia and *O. talaje*, I have no doubt, might play a similar part in Mexico and Central America whence I have received specimens. Lately, both Leishman and myself have received specimens of *O. tholozani* from Quetta, India, where it was suspected of being a vector, but experiments carried out with the few living examples which reached Leishman have proved negative. Again, from the fact that *Argas persicus*, as tested experimentally by Sergent and Foley (1908) in the Sud-Oranais, Africa, serves as a host for spirochaetes of human origin, we may conclude that this species, which frequently attacks man, may also communicate relapsing fever under suitable conditions. Sergent and Foley found the spirochaetes present in the coelomic fluid of this tick for two days, after which they disappeared.

That neither the tick nor the spirochaete are specifically adapted to each other is a matter of considerable importance which has been revealed by recent research. In view of the morphological similarity of the supposedly different species of spirochaetes and their individual variations in virulence, we may well doubt if many of the "species" are valid. As I pointed out four years ago, the various specific names given to the spirochaetes causing relapsing fever in man may be used merely for convenience to distinguish strains or races of different origin.\* They cannot be regarded as valid names, in the sense of scientific nomenclature, for virulence and immunity reactions are not adequate tests of specificity. Under experimental conditions *O. moubata* has served for the transmission not only of *S. duttoni* and two other so-called species, *S. recurrentis* and *S. novyi*, which affect man in the Old and New World respectively, but it has also been found to transmit the fowl spirochaete. *S. duttoni*, moreover, has been successfully transmitted to rats by *Hemulopinus spinulosus*, the common rat-louse. There is every reason to suppose that a spirochaete capable of adapting itself either to a tropical African tick or to a rat-louse occurring all over the world, will

be able to accommodate itself to a variety of vertebrate hosts; and we know in fact, from laboratory tests, that a considerable number of animals are susceptible to infection with *S. duttoni*, various species of monkeys, rats, mice, rabbits, guinea-pigs, sheep, goats, horses, and dogs, etc., having been successfully infected.

#### TRANSMISSION OF RELAPSING FEVER BY PEDICULUS AND CIMEX.

It has long been supposed that vermin are responsible for the transmission of relapsing fever in Europe. Flügge (1891) appears to have been the first scientific writer to suggest this possibility, and Tictin (1897) supposed that bugs (*Cimex lectularius*) might transmit the disease by their bites or by being crushed and their contents entering the skin through excoriations due to scratching. He infected monkeys with the contents of bugs removed 24 hours after they had fed on relapsing fever blood. Karlinski (1902) and likewise Schaudinn observed the survival of spirochaetes in bugs for 30 days or more. Christy (1902) and Breinl, Kinghorn, and Todd (1906) failed to transmit spirochaetosis by bugs. In experiments of my own (1907) it was found that *S. duttoni* survived six days in the bug at 12° C., but only for six hours at 20-24° C. Similar results were obtained by *S. recurrentis* (from Russia). The parasites appeared to be merely digested by the bug, the rate of digestion being governed by the temperature at which the insects were maintained. In but one experiment did I succeed in transmitting relapsing fever to a mouse by means of bugs. In this case I used 35 of the insects, and transferred them directly from an infected to an uninfected mouse, interrupting their feed upon the first animal and allowing them to complete it upon a second clean mouse. We may, therefore, conclude that bugs can occasionally transmit relapsing fever.

We have, on the other hand, conclusive proof that lice are concerned in the transmission of the disease. The first important evidence in this connection dates from Mackie (1907), in India. This author records an outbreak of relapsing fever amongst school children, in which 137 out of 170 boys and 35 out of 114 girls, were attacked. The boys were found to be more infested with vermin than were the girls. An examination of the lice removed from the boys showed 24 per cent of them to contain spirochaetes, whereas only 3 per cent of the lice collected from the girls contained these micro-organisms. As the epidemic increased among the girls their verminous condition became more evident, as the epidemic decreased among the boys the lice were found less frequently upon them. Mackie noted that the spirochaetes multiplied within the gut of the lice and that they could be found in the ovary, testis, and Malpighian tubules of the insects. He concluded that infection might result from the insects regurgitating the contents of their alimentary canal into the wound in the act of feeding.

Sergent and Foley (1908) next observed the presence of *Pediculus vestimenti* upon the persons of nearly all patients affected with relapsing fever in Sud-Oranais, North Africa,

\* *S. recurrentis* may be the only true species; the name *recurrentis* has priority over *S. obermeieri*. Other so-called species are *duttoni*, *rossi* or *kochi*, *novyi*, *berbera*, *carteri*, etc.

and they observed spirochaetes in the bodies of the lice. Subsequently (1910), they found these lice associated with every case they observed in Algeria.

The most convincing observations are, however, those published in a short paper this year by Nicolle, Blaizot, and Conseil (1912). They note, in respect to its epidemiology, that relapsing fever affords a striking similarity to typhus fever. The disease extends in a similar manner, it occurs in the same places, when it enters hospitals it does not spread, sparing the nurses and physicians who have to deal with the patients who have been cleansed, whereas it attacks those who have to handle the patients at their entry into the hospital. In both diseases, as observed in Tunisia, lice are invariably found on the patients.

Nicolle and his colleagues obtained negative results when they attempted to transmit the disease through the bites of infected lice placed upon experimental monkeys and five persons (two of whom were the authors), although both men and monkeys were exposed to thousands of bites collectively. Upon studying the behaviour of the spirochaetes in the lice (*P. vestimenti* and *P. capitis*), they found that they disappear and afterwards reappear. But few can be detected in the gut five to six hours after the infective feed, and none are discoverable microscopically when 24 hours have elapsed. After about 8 to 12 days, however, actively motile spirochaetes reappear in the louse; at first they are short, but later they resemble those seen in the blood. Such spirochaetes are observable in lice up to the 11th day, and possibly longer. Monkeys inoculated with the contents of lice, crushed on the 15th day after the infective feed, developed relapsing fever.

We know that all persons infested with lice are addicted to scratching themselves, whereby they excoriate their skin and frequently crush the lice upon their bodies. In this manner their hands and finger-nails become infected with the body contents of the lice including the spirochaetes, and these gain a ready entrance through the excoriated skin, thereby infecting the individual. One of the authors, having excoriated his skin, smeared the contents of an infected louse upon the lesion, and succeeded thereby in infecting himself, the disease developing after a period of incubation lasting five days. In one experiment, infection followed the placing of the contents of a louse upon the conjunctiva in man. In nature, it might well happen that the soiled hand might travel to the eye and produce infection in a similar manner. The authors proved, moreover, that the spirochaetes are transmitted hereditarily to the offspring of the infected lice, for they found that eggs, laid 12 to 20 days after the infection of the parent lice, contained the spirochaete. The larvæ issuing from these eggs likewise contained spirochaetes. By incubating the eggs at 28° C., the larvæ hatched out on about the seventh day. When the eggs or larvæ were crushed and inoculated into a monkey the latter became infected.

We still lack detailed information regarding the behaviour of the spirochaetes in the lice and their offspring; possibly it is similar to that recorded for *S. duttoni* in *O. moubata*. The main point may, however, be now regarded as established

that lice (both *P. vestimenti* and *P. capitis*) transmit relapsing fever and are presumably the ordinary vectors in most parts of the world. These discoveries are naturally of the greatest practical importance, in view of the prevention of relapsing fever.

I shall here digress to say a few words about the biology of lice infesting man, since you will find no precise information about it in the literature, except for the observations made by my demonstrator, Mr. Cecil Warburton, in Cambridge. The latter has made the only accurate observations hitherto recorded for *Pediculus vestimenti* in conjunction with an investigation we undertook on behalf of the Local Government Board, the results of which were published in their reports for 1910. Mr. Warburton found that *P. vestimenti* (= *corporis*) lives longer than *P. capitis* under adverse conditions. This is doubtless due to its living habitually on the clothing, whereas *capitis* lives upon the head where it has more frequent opportunities of feeding. He reared a single female upon his own person with self-sacrificing enthusiasm, keeping the louse enclosed in a cotton-plugged tube with a particle of cloth to which it could cling. The tube was kept next to his body, thus simulating the natural conditions of warmth and moisture under which these creatures thrive. The louse was fed twice daily whilst it clung to the cloth upon which it rested. The female lived one month. She copulated repeatedly with a male which died on the 17th day, and was replaced by a second male which likewise entered into copulation and survived the female. Copulation commenced five days after the female emerged and the process was repeated a number of times, sexual union lasting for hours. The female laid 124 eggs within 25 days. The eggs hatched after eight days under favourable conditions, such as those under which the female was kept; they did not hatch in the cold. Eggs kept near the person during the day and hung in clothing by the bedside during the winter in a cold room, did not hatch until the 35th day. When the larvæ emerge from the egg they feed at once if given a chance to do so. They are prone to scatter upon the person and abandon the fragment of cloth to which the adult clings. The adult stage is reached on the 11th day after three moults occurring about every fourth day. Adults enter into copulation five days after the last ecdysis. The adults reared by Mr. Warburton lived about three weeks after the final moult, and the "egg to egg" period is reckoned at about 24 days. Unfed *P. vestimenti* adults died quickly at any temperature; only one specimen survived in a feeble condition until the fifth day. Unfed larvæ died in 36 hours.

To this we may add that Nicolle and his colleagues find that both *P. vestimenti* and *P. capitis* survive longest when maintained at 28° C., in a damp atmosphere, being fed twice a day.

I have allowed myself this digression, dealing with *Pediculi*, because Warburton's results are doubtless unknown to many and these parasites have only lately crept—not sprung—into prominence especially with regard to the etiology of typhus fever and relapsing fever.



It is of importance to note how long the eggs may survive in view of the hereditary transmission of the spirochaetes in lice. It is obvious that the disinfection of verminous clothing is indicated as a preventive measure, and that those coming in contact with patients suffering from these diseases should promptly change their clothing and inspect their persons carefully after exposure with a view to avoiding the bites of infected lice.

#### SPIROCHAETOSIS IN CATTLE.

The discovery of spirochaetosis in cattle is due to Theiler after whom the causative agent, *S. theileri*, has been named. The parasite is transmitted by the tick *Boophilus decoloratus* in Africa (Fig. 9). Laveran and Vallée, to whom Theiler sent the infective ticks, reproduced the disease experimentally in France. That the ticks in this case become infected hereditarily goes without saying, for the infective ticks used by the French authors were larvæ hatched from eggs laid by females

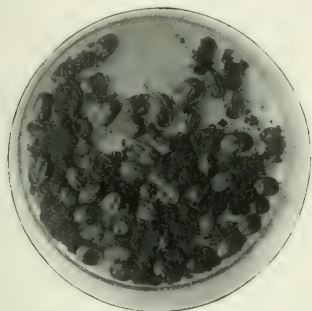


FIG. 9.—*Boophilus decoloratus*, ovipositing females.

which had fed on cattle harbouring the spirochaetes in South Africa. We lack observations to show if the ticks may remain continuously infective through several generations, as seen in *S. duttoni*-infected *O. moubata*. About 14 days after such infective larvæ are placed upon cattle, the latter develop spirochaetosis, but the infection appears to be mild. In Laveran and Vallée's experiment spirochaetes were only present in the blood for four days. Four days later, however, the animal developed piroplasmosis, proving that the ticks had transmitted a double infection. Koch, working in Africa in the same year (1905), likewise observed spirochaetosis in cattle and reported finding the spirochaetes in the eggs of a species of tick which he found upon the affected animals.

This exhausts the list of spirochaetes concerning whose mode of conveyance we have definite knowledge. There are, however, a number of different animals infected by spirochaetes which are doubtless transmitted in a similar manner. Horses occasionally harbour spirochaetes, and so do sheep in Africa, and, judging from inoculation experiments, these spirochaetes are probably identical with *S. theileri*. Bats, as

Nicolle and Comte found in Northern Africa, suffer from a typical relapsing fever due to *S. vespertilionis* which may be conveyed by several of the numerous ectoparasites infesting these animals; *Argas vespertilionis* and lice would naturally suggest themselves to me as being the probable vectors. *Spirochaeta muris*, occurring in rats and mice, and *S. gundi* Nicolle, 1907, occurring in a small African rodent (*Ctenodactylus gundi*) are both transmissible by blood inoculation and presumably in nature are transmitted by ectoparasitic arthropods.

#### CULTIVATION OF SPIROCHAETES.

Another important step in our knowledge concerning spirochaetes is that they can be cultivated in vitro. All efforts to cultivate them under ordinary conditions, suitable for the great majority of bacteria, have given negative results in the hands of many bacteriologists all over the world. Levaditi (1906), it is true, succeeded in cultivating *S. gallinarum* and *S. duttoni* in collodion sacks placed, according to the usual technique, in the peritoneal cavity of rabbits. Under these conditions the spirochaetes multiplied and lived for 73 days or more. Successful cultivation in vitro has, however, only been recently accomplished by Noguchi (August, 1912), by adding a few drops of citrated rat or mouse blood, containing the spirochaetes, to sterile ascitic or hydrocele fluid (10 to 15 cc.) in tubes containing pieces of freshly excised rabbit's kidney. Precautions against bacterial contamination are imperative; it is best to collect the infected blood at the 48th to the 72d hour of the disease, and the tubes should be maintained at 36° C. He experimented with *S. duttoni* and two strains of *S. recurrentis* which he calls *kochi* and *obermeieri*. *S. duttoni* was still virulent after the ninth transplantation; *S. kochi* was transplanted 29 times, subcultures being made every four to nine days, the maximum growth being attained about the ninth day. This strain appeared to lose its virulence by prolonged culture. *S. obermeieri* attained its maximum growth on the seventh day, and was still virulent after having attained the seventh subculture.

To sum up, then, we have represented in the blood-inhabiting spirochaetes of warm blooded animals a group of micro-organisms which, under natural conditions, are mainly conveyed by blood-sucking ectoparasites within which they undergo a process of development and in which they are hereditarily transmitted. Spirochaetes are not specialized parasites. Infection may take place through the skin or mucous membrane to which the spirochaetes gain access by being deposited thereon in the arthropod's dejecta or by the infested individual scratching or rubbing himself with hands which have become contaminated with the contents of the vermin which they have crushed. The lesions produced by the bites of the arthropods and the excoriations inflicted upon the individual by himself greatly facilitate the entrance of the spirochaetes.

# FURTHER STUDIES ON THE RÔLE OF THE HYPOPHYSIS IN THE METABOLISM OF CARBOHYDRATES.

## THE AUTONOMIC CONTROL OF THE PITUITARY GLAND.\*

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### SYNOPSIS.

1. Introductory.
2. Hypophysial versus bulbar (Bernard) punctures.
3. Experiences with stimulation of superior cervical ganglion.
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  - b. After division of both sympathetic cords and vagi.
  - c. After division of the splanchnic nerves.
  - d. After spinal cord transection at T. IV segment.
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6. Summary.
7. Conclusions.

Appendix. The significance of "available glycogen."  
Glycosuria following spinal cord transection.

### I. INTRODUCTORY.

In a former paper from the Hunterian Laboratory in Baltimore<sup>2</sup> it was stated that: *In view of the ease with which hyperglycemia may be produced by hypophysial lesions it is possible that our views in regard to the glycosurias of supposedly encephalic origin need some revision.* The present communication deals with certain studies pursued in this direction.

It had been observed that a transient glycosuria and polyuria were of common occurrence after a canine hypophysectomy, whereas after the same operative procedure, provided it stopped short of the manipulation of the hypophysial stalk necessary for a total removal, sugar was rarely, if ever, present. The presumption, therefore, was a natural one, in view of the glycogenolysis which follows the administration of glandular extracts, that the manipulation had led to a discharge of secretion. In this connection, moreover, it was assumed that the glycosurias and polyurias which not uncommonly follow fractures of the cranial base were possibly due to a contusion of the pituitary body itself, rather than to an excitation of some one of the various predicated glycosuric or diuretic centers.

### 2. EXPERIENCES WITH BERNARD AND HYPOPHYSIAL PUNCTURES.

Some inquiry among physiologists who, for one purpose or another, had employed a Bernard piqûre in their investiga-

tions, showed that there was considerable disagreement as to the most effective site for the puncture, and in one preserved specimen it was seen that the needle had been introduced above the tentorium, and the end of its track lay suspiciously near the infundibulum. Hence, in the spring of 1911, some tentative studies of this matter were made by W. E. Dandy and Henry Fitzsimmons in the Hunterian Laboratory.

As in Bernard's original studies,<sup>3</sup> the observations were made on rabbits. Under primary anesthesia (ether in amounts insufficient to cause glycosuria) a sterile copper wire of measured length was introduced to the proper depth through a primary cranial perforation. The wire was left *in situ*, so that the track could subsequently be identified. The method was controlled by making certain lateral punctures, which showed that the mere insertion and subsequent carrying of the wire would cause no symptoms of irritation or discomfort.

Our object was to compare the effect of a Bernard piqûre of the supposed sugar center in the fourth ventricle with one which entered the pituitary fossa itself. After some anatomical studies, it was found, for the purpose of an hypophysial piqûre, that the wire could be introduced from a median frontal position and passed along the ethmoidal groove to the sella turcica.

Not all of the experiments were successful—for reasons which at the time were not apparent ("available glycogen," etc.). Some fairly typical Bernard punctures failed to give glycosuria, and one typical hypophysial puncture gave a negative result; also a number of atypical (lateral or too short) Bernard piqûres gave actual glycosuria, and one merely an extreme diuresis. However, two or three of these preliminary observations may be recorded, for the sake of the chronology of our story.

The following is an example of a fairly typical puncture of the Bernard type producing glycosuria:

No. XVI. June 23, 1911. Male rabbit. A pre-operative catheter specimen of urine gave no reduction of Fehling's solution.

10.30 a. m. Through a median cranial perforation just caudal to the tentorium the wire was passed for a distance of 1.6 cm towards the floor of the fourth ventricle and cut off extracranially. Prompt recovery. At 3 p. m. 3 cc. of urine obtained by catheter gave marked reduction of Fehling's solution.

June 24, a. m. Urine obtained on catheterization continued to give a reduction of Fehling's solution.

June 25, a. m. A catheter specimen showed absence of reducing substance.

June 26. Urine gave no reduction by Fehling's solution. Animal sacrificed at 9.30 a. m.

The *post mortem* examination revealed a median piqûre, the

<sup>2</sup>Claude Bernard: *Leçons de physiol. exper.* (Cours de semestre d'hiver.) Paris, 1855. Also: *Leçons sur le physiologie et la pathologie du système nerveux.* Paris, 1858.

\* Presented at the meeting of the American Physiological Society, Cleveland, December 30, 1912.

<sup>1</sup>These studies were for the most part made during the past year or two in the Hunterian Laboratory of the Johns Hopkins University.

<sup>2</sup>Goetsch, Cushing and Jacobson: Carbohydrate tolerance and the posterior lobe of the hypophysis cerebri. *BULL. JOHNS HOPKINS HOSP.*, 1911, xxii, 165-190.

wire passing slightly backward from the exact perpendicular to the surface of the skull. The wire had penetrated the mid-cerebellum; it had entered the brain stem to an unnecessary depth, extending half way through the pons. Its position in the fourth ventricle was slightly cephalic to Bernard's point. There was practically no evidence of traumatic extravasation along the course of the wire and no inflammatory reaction.

The following is an example of a successful *hypophysial* puncture producing glycosuria:

No. XVIII. June 28, 1911. Female rabbit. Urine before operation showed no reduction of Fehling's solution. At 11.30 a.m., through an anterior cranial perforation a wire was passed into the sella, with presumable accuracy. The slight external bleeding was easily checked. At 5 p.m. a specimen of urine obtained by catheter reduced Fehling's solution.

June 29. At 9 a.m. the urine gave no reduction of Fehling's solution. Animal sacrificed. At autopsy the wire was found to pass directly backward into the pituitary fossa. The gland was much ecchymosed. There was practically no extravasation along the track of the wire.

We had begun to have some inkling of a possible control by the so-called sugar center of Bernard over the discharge of a substance from the gland capable of glycogenolysis, and a few experiments were made with this in mind. The following is an example of the *double punctures* (a primary Bernard and secondary hypophysial, or the reverse) which were performed:

No. XIV. June 21, 1911. Male rabbit. Urine by catheter before operation showed no reducing body by Fehling's test. At 11 a.m. both cervical sympathetics were cut, with characteristic vaso-dilatation of ear vessels, narrowing of the pupils, etc. At 12 m. a Bernard piqûre was made, without complications. A catheter specimen obtained a few moments before the puncture showed no reducing body. At 2.05 p.m. the urine gave a marked reduction of Fehling's solution.

June 22, a.m. Urine voided during night proved negative for reducing bodies by Fehling's solution. Rabbit in good condition.

June 23. Urine gave no reduction of Fehling's solution.

June 24. Morning urine showed continued absence of reducing substance. At 10.45 a.m. *hypophysial puncture* performed under primary ether. At 12 m. urine obtained by catheter showed abundance of sugar.

June 25. Collected urine gave no reduction.

June 26. Urine obtained by catheter gave no reduction of Fehling's solution. Animal sacrificed at 9.35 a.m.

On *post mortem examination* the Bernard piqûre was found to pass through the cerebellum at the proper angle, the tip of the wire having barely reached the floor of the fourth ventricle. In the case of the hypophysial piqûre the wire had impinged on the floor of the sella turcica. There was evidence of some extravasation along the path of this second wire and also in the pituitary body itself, but there were no apparent ecchymoses in the tuber cinereum.

As our subsequent experiences have taught us, an experiment of this type would only have been conclusive had the spinal cord as well as the cervical sympathetics been divided before the punctures, and time allowed for the reaccumulation of glycogen. Under these conditions, as will subsequently be shown, the Bernard piqûre should not, and the hypophysial piqûre should, have given glycosuria. These early experiments, therefore, merely served to show that an hypophysial puncture would discharge glycogen as readily as would a typical Bernard piqûre.

If the contention of our predecessors, that the pars nervosa of the hypophysis plays an important rôle in the carbohydrate mechanism of the body, were to prove correct, it seemed not unlikely that a medullary piqûre of the Bernard type would serve to discharge the secretion of the posterior lobe in the same manner that such an impulse is believed to liberate the active principle of the adrenals.

Some studies (unpublished) by W. E. Dandy demonstrated the presence of non-medullated fibers coursing from the carotid plexus into both lobes of the pituitary body. These fibers accompany the vessels which he and Goetsch described 'as constituting the essential circulation of the organ. This histological demonstration of a sympathetic nerve supply to the gland spoke in favor of a possible nervous influence over its secretion. It had been suggested, moreover, that the inevitable glycosuria which occurred in a series of rabbits used for testing hamodynamic responses for cerebrospinal fluid might have been due to the trauma and excitation of the cervical sympathetic trunk during the exposure of the carotid artery for attachment to the kymographion, rather than to the presence in the fluid itself of posterior lobe secretion.

### 3. EFFECT OF STIMULATING THE SUPERIOR CERVICAL SYMPATHETIC GANGLION.

With these possibilities in mind, some preliminary tests were carried out to ascertain if the assumption of a nervous control over the pituitary body would endure. It was found (first in the case of the rabbit) that when the cervical sympathetic cord<sup>4</sup> was traumatized by repeated manipulations there was no subsequent occurrence of glycosuria. When, however, the dissection of the cervical sympathetic was carried higher in the neck, namely, to the superior cervical ganglion, sugar in large amounts promptly appeared in the urine. The record of a typical experiment showing this phenomenon follows:

PROTOCOL I. *Faradic stimulation*<sup>5</sup> of right superior cervical ganglion: resultant glycosuria.

July 26, 1911. Large adult female cat. 1.30 p.m. Administration of ether begun. Urine obtained by catheter showed absence

<sup>4</sup>Dandy and Goetsch: The blood supply of the pituitary body. *Am. Jour. Anat.*, 1910-11, xi, 137.

<sup>5</sup>It may be well to recall the anatomical variations of the cervical sympathetic trunk in the three species of laboratory animals used in the experiments. In the neck of the *dog* and *cat* the vagus and sympathetic cord lie in the same sheath. As one traces this vago-sympathetic trunk upward in the *cat*, the sympathetic fibers leave the vagus anteriorly, to expand into the superior cervical ganglion, which lies just anterior to the lower ganglion of the vagus. In the *dog* the vagal ganglion and the superior cervical ganglion exist in close association, with, however, a line of cleavage clearly visible between them. On dissection the two ganglia are found to be connected only by a rather heavy bundle of fibers. The cervical sympathetic trunk in the *rabbit* is entirely separated from the vagus: in some of the animals, moreover, the sympathetic fibers run in two separate bundles on both sides of the neck. The superior cervical ganglion is connected with the ganglion of the vagus by a delicate fiber strand.

<sup>6</sup>It may be noted here that in all of these experiments the method of bipolar stimulation was used, with a current which could be borne on the tongue.



of sugar by Fehling's and Nylander's tests. The superior cervical ganglion was exposed and isolated by gauze dissection. Bipolar faradic stimulation of ganglion by weak, moderate, and fairly strong currents at intervals for twelve minutes. Marked pupillary dilatation occurred during stimulation.

2 p.m. Etherization ended. Urine obtained by catheter gives marked reduction of Fehling's and Nylander's solutions. On fermentation sugar was found to be present in amounts of over 1 per cent. Reading on polarization; dextro, 1.8 per cent.

This basic experiment showing that *stimulation of the superior cervical ganglion causes a prompt and outspoken glycosuria* we have found to hold true in forty observations on the cat, rabbit and dog, the one requisite for the glycosuria being the presence of what we will fully describe later on as "available glycogen." Needless to say, the amount of ether required for anaesthetization, as shown by control experiments, has been far from sufficient to account for the glycogenolysis.

Cats and rabbits have been used for the most part, on account of the ease with which the ganglion may be exposed in these animals; but the essential phenomenon has been confirmed sufficiently often on dogs to show that the same response occurs in this species. It may be said, however, that the glycosurias of the dog have proved to be less prompt in occurrence and of a lower sugar percentage than those of the cat and rabbit. This may perhaps be explained on the ground that the same strength of stimulus was employed in all cases, and it may not have been of sufficient intensity to occasion an equal glycosuria in the larger animal. The results, moreover, may have been somewhat modified by the fact that specimens of canine urine were not obtained until the animals voided; whereas in female cats and in both male and female rabbits catheterization was resorted to.

In the preceding protocol the glycosuria would naturally be attributed to the faradic excitation. It has been demonstrated, however, in subsequent experiments on cats and rabbits that other forms of stimulus suffice to cause the prompt appearance of sugar in the urine. The following is one of many experiences which show that the mere manipulation of the superior cervical ganglion essential to the free dissection of the structure may provoke glycosuria:

**Protocol IX. Mechanical stimulation of vagus and sympathetic trunk: no glycosuria. Subsequent exposure of the right superior cervical ganglion: prompt glycosuria.**

August 4, 1911. Large female rabbit. 3.45 p.m. Urine obtained by catheter gave no reduction of Fehling's solution. Under local anaesthesia the right vagus was exposed and mechanically stimulated many times, the sympathetic trunk meanwhile being walled off by rubber protective.

4.20 p.m. Urine obtained by catheter (30 minutes after the traumatic stimulation of the vagus) negative for sugar by Fehling's solution.

4.25 p.m. The right sympathetic trunk was subjected to a repeated mechanical stimulus in like fashion, and thirty minutes later (4.55 p.m.) a catheterized specimen of urine showed no sugar.

5 p.m. The superior cervical ganglion was freely exposed by carrying the dissection higher in the neck, and thirty minutes later (*viz.* 5.43 p.m.) the urine, obtained by catheterization, gave marked reduction of Fehling's solution.

August 5. 9 a.m. Urine (catheter specimen of 15 cc.) gave no reduction of Fehling's solution. Repetition of stimulation of the superior cervical ganglion failed to evoke a second mellituria.

The preceding record indicates that the mere exposure by dissection of the superior cervical ganglion may elicit a marked glycosuria, whereas intentional traumatic manipulation of the pre-axial sympathetic fibers, as well as of the vagus, may not suffice to produce this effect.

On ascertaining that stimulation of the superior cervical ganglion in dogs, cats and rabbits caused a marked glycogenolysis, the problem of the finer relationship of the fibers in the sympathetic trunk to this phenomenon naturally called for investigation.

The cervical sympathetic system originates in pre-ganglionic fibers which emerge in the ventral roots from the lowest cervical to the third thoracic spinal segment. These pre-ganglionic fibers for the most part course through the inferior to the superior cervical ganglion. From the latter structure the pathway is continued onward by post-ganglionic fibers, the nerve cells with their essential synapses lying in the ganglion.

With such a conception of the cervical sympathetic system, it seemed unlikely that the glycosuria from stimulation of the ganglion could have been due to an excitation of nerve fibers passing in the direction of the inferior ganglion, whence they might enter the spinal cord or continue to the abdominal viscera.

(a) *After Section of the Pre-ganglionic Fibers.*—As exemplified in the foregoing protocol, traumatization of the sympathetic cord in the neck of a rabbit failed to produce a glycosuria, and in subsequent more carefully executed experiments even faradic stimulation was found to be equally ineffectual. With the belief that the impulses controlling the superior cervical ganglion must ascend in this cord, we carried out a series of experiments on rabbits, in which, after sectioning the cervical sympathetic (a procedure which in itself does not result in glycosuria), the lower proximal end of the divided nerve was stimulated by the faradic current. Ascertaining that this excitation caused no mellituria, the upper cephalic end of the divided sympathetic nerve was stimulated in like manner. As no sugar appeared in the urine after this second procedure, faradic excitation was supplied to the superior cervical ganglion, with a resultant prompt glycosuria. The data of such an experiment follow:

**Protocol XLVIII. Faradic stimulation (peripheral and central) of divided pre-ganglionic cord: no glycosuria. Stimulation of homolateral superior ganglion: prompt glycosuria.**

May 1, 1912. Small adult male rabbit. 11 a.m. A catheter specimen of urine negative for sugar by Fehling's and Nylander's tests.

11.15 a.m. Section of right sympathetic cord in neck. Faradic stimulation (coil at 6 cm.) of lower proximal end of divided right sympathetic trunk for three intervals of 30 seconds each, with intermissions of the same period.

2 p.m. Catheter specimen (17 cc.) of urine: negative for sugar (Fehling and Nylander).

2.10 p.m. Similar stimulation of upper distal end of divided right sympathetic cord.

4.20 p.m. On catheterization 15 cc. of urine obtained: negative Fehling's and Nylander's tests.

4.30 p.m. Exposure of right superior cervical ganglion.

4.38. Faradic stimulation (coil at 6 cm.) of right superior cervical ganglion for three intervals of 30 seconds, as above.

4.45 p.m. Closure of wound.

5.10 p.m. Urine on catheterization, 10 cc., with a marked reduction of Fehling's and Nylander's solutions.

May 2. Animal in normal condition. 9 a.m. Urine (catheter specimen) negative for sugar (Fehling and Nylander).

Believing that possibly the fibers in the distal (cephalic) trunk might have lost their excitability during the interval of three hours between the first and second excitations, the procedure recorded above was modified as follows. The sympathetic cord on one side was sectioned and its lower proximal end stimulated. Then, after allowing sufficient time for a possible reducing body to appear in the urine, the sympathetic cord on the opposite side was divided and its upper distal extremity immediately stimulated. In this way the possibility of loss of excitability in the cords from exposure was eliminated, but the procedure failed to give mellituria until the superior cervical ganglion was stimulated. The protocol of such an experiment follows:

**PROTOCOL LVI. Faradic stimulation (central left, and peripheral right) of divided pre-ganglionic cords: no glycosuria. Stimulation of right ganglion: eventual glycosuria.**

May 13, 1912. Adult female rabbit. 10 a.m. Catheter specimen of 4 cc. negative by Fehling's and Nylander's tests.

10.05 a.m. Section of left sympathetic trunk in middle of neck.

10.07 a.m. Faradic stimulation (coil at 6 cm.) of lower proximal end of divided left sympathetic trunk for three intervals of 30 seconds each, with intermissions of the same period.

10.13. Closure completed.

12.55 p.m. By catheter, 16 cc. of urine, giving no reduction of Fehling's or of Nylander's solution.

1 p.m. Section of right sympathetic trunk in middle of neck.

1.05 p.m. Corresponding faradic stimulation (coil at 6 cm.) of upper distal end of divided right sympathetic trunk.

1.14 p.m. Closure completed.

3.35 p.m. Urine by catheter (18 cc.) negative for sugar (Fehling's and Nylander's).

3.45 p.m. Exposure of right superior cervical ganglion begun.

3.50 p.m. Faradic stimulation (coil at 6 cm.) of right superior cervical ganglion for three intervals with intermissions of 30 seconds each.

4 p.m. Closure completed.

5 p.m. Catheterization unsuccessful.

May 14, 10 a.m. Catheterization unsuccessful.

4.30 p.m. Clear specimen of urine obtained by catheter: marked reduction of Fehling's and Nylander's solutions.

The following conclusions may be drawn from these two typical protocols: (1) That faradic stimulation applied to the cervical sympathetic cord is ineffectual as an agent for producing mellituria, and (2) that excitation of the superior cervical ganglion gives a positive result and causes sugar to appear in the urine even when both sympathetic cords are divided in the neck.

Two possible explanations of this failure to elicit glycosuria by stimulation of the pre-ganglionic cord are as follows: The first and more probable is that degenerative changes in the non-medullated fibers occur with such rapidity at the points of

contact with the electrodes that they cease to conduct an adequate stimulus. A less probable explanation is that heretofore undescribed pre-ganglionic fibers, stimulation of which leads to glycosuria, leave the spinal cord high in the cervical region and make some direct connection with the superior cervical ganglion.

(b) *After Division of the Vago-Sympathetic Trunk.*—In so far as the positive results from stimulating the ganglion itself are concerned, the question arises, does the excitation applied to the ganglion affect centripetal fibers leading to some glycogenolytic center, or are we dealing with the efferent side of a reflex which exhibits its end result by the presence of sugar in the urine? If the former, it might be conceived that the impulse travels to the cerebrospinal axis cephalad along the internal carotid artery or along one of the cervical nerves, or even downward along the vagus or sympathetic trunk to enter the cord at a lower level.

The foregoing protocol speaks against the view that the impulse travels downward along the sympathetic trunk; for in these experiments on rabbits excitation of the ganglion gave rise to glycosuria even with a divided cervical sympathetic cord. In the cat, moreover, the sympathetic cord runs in the same perineurilemma with the vagus, and stimulation of the superior cervical ganglion in this animal is effective even after section of this combined vago-sympathetic trunk. Such an experiment follows:

**PROTOCOL VII. Preliminary section of vago-sympathetic trunk: stimulation of superior cervical ganglion: subsequent glycosuria.**

August 4, 1911. Small male cat. 2.18 p.m. Etherization begun.

2.24 p.m. Exposure of vago-sympathetic trunk: urine then obtained by abdominal pressure negative for sugar by Fehling's solution.

2.29 p.m. Right vago-sympathetic trunk sectioned in middle of neck.

2.44 p.m. Right superior cervical ganglion exposed by dissection. Etherization ended.

3.14 p.m. Urine gave marked reduction of Fehling's solution.

4.30 p.m. Urine gave positive reduction of Fehling's solution.

August 5, 9.50 a.m. Urine negative for sugar by Fehling's solution.

In subsequent experiments it was found that stimulation of the superior cervical ganglion invariably provoked glycosuria after both vagi and the two sympathetic trunks in the neck had been sectioned. It was ascertained also that stimulation of the ganglion after it had been freed from all its connections except the distal cephalic trunk along the internal carotid artery likewise caused glycosuria. This was demonstrated in many experiments on the dog, cat and rabbit; but inasmuch as the mere exposure of the structure by dissection may cause glycogenolysis, the observations were not conclusive, for sufficient excitation might already have passed from the ganglion along some other connections to give rise to the hyperglycemia and subsequent glycosuria.

(c) *After Division of the Splanchnic Nerves.*—Having excluded the possibility of an impulse passing downward from the ganglion, our next step was to eliminate the chance that a centripetal impulse passed to the cord or to the brain stem.

Assuming that these glycosurias are due to the discharge of hepatic glycogen through neurogenic impulses, it was believed that a reflex through the central nervous system could be excluded either by section of all nerves to the liver or by division of the spinal cord cephalad to the superior limit of the origin of the splanchnic nerves, the relation of which to the glycosurias of hepatic and adrenal origin Macleod<sup>7</sup> has so well shown.

Thus we first endeavored to eliminate this possibility of some unknown nervous connection between the superior cervical ganglion and the liver by preliminary division of all the autonomic fibers in the gastro-hepatic ligaments. The results served merely to corroborate, in the cat, Macleod's observations made on the dog. As no animals survived in whom the urine became sugar free we were unable to test the effect of a subsequent stimulation of the superior cervical ganglion.

(d) *After Transection of the Spinal Cord.*—It became necessary therefore to resort to the second possible method of excluding a splanchnic course of the impulse—namely, the complete transverse section of the spinal cord above the splanchnic nerves.

To our surprise, this procedure almost invariably gave rise to a glycosuria in the animals used (dog, cat and rabbit). Fortunately, however, these glycosurias from spinal transection as a rule proved to be of short duration, the urine of the animals soon becoming sugar free. It was found, moreover, that if food was withheld after section of the cord above the splanchnics (*i. e.*, on a level with the fourth pair of thoracic nerves), neither stimulation of the superior cervical ganglion nor of the splanchnic fibers in the gastro-hepatic ligament, nor a second division of the cord, would elicit glycosuria. This as we found in the course of time, is due to the fact that, in response to the primary stimulus, all the available glycogen of the body has been discharged in the form of dextrose; for by the judicious feeding of these animals a second mellituria of extreme degree may be caused by any of the stimuli which prove effective in the normal animal.

The details of a typical experiment illustrating this reaccumulation and redischARGE of glycogen are given below:

PROTOCOL XXVIII. *Preliminary spinal cord transection with glycosuria: reaccumulation of glycogen: secondary glycosuria following stimulation of superior cervical ganglion after division of vago-sympathetic cord.*

For four days previous to beginning the experiment the animal, a large female cat, was confined and abundantly fed. At no time did the urine show sugar.

December 19, 1911, 9.45 a.m. Etherization begun.

10 a.m. Urine on catheterization negative for sugar by Fehling's solution.

10.15 a.m. Laminectomy performed: complete transverse division of spinal cord at fourth thoracic segment.

10.30 a.m. Operation completed. Urine by catheter gave marked reduction of Fehling's solution.

5.45 p.m. On catheterization, urine still showed strong reducing qualities to Fehling's solution.

December 20, 8.30 a.m. Animal in good condition. On catheterization 50 cc. of urine obtained: negative for sugar by Fehling's solution.

9 a.m. Animal given by stomach tube 100 cc. of milk, warmed to body temperature, containing 20 grams of saccharose.

12.45 p.m. Urine by catheter gave slight reduction of Fehling's solution.

2.40 p.m. Animal given 100 cc. of warm milk containing 5 grams of saccharose.

December 21, 8.30 a.m. Urine by catheter gave slight reduction of Fehling's solution.

12.45 p.m. Urine by catheter negative for sugar by Fehling's and Nylander's tests.

1.30 p.m. Etherization begun.

1.45 p.m. Section of right vago-sympathetic cord in neck before exposure of right superior cervical ganglion. Faradic stimulation (coil at 8 cm.) of ganglion intermittently for fifteen minutes (ten stimulations of ten seconds each).

2 p.m. Etherization ended.

2.15 p.m. Urine on catheterization gave marked reduction of Fehling's and Nylander's solution.

5 p.m. A few drops of urine, obtained by catheter, gave marked reduction of Fehling's solution.

December 22, 10.30 a.m. Urine by catheter (50 cc.): no reduction of Fehling's solution.

2.30 p.m. Urine on catheterization (15 cc.) gave no reduction of Fehling's or Nylander's solution. Animal died under the anæsthetic given preparatory to second stimulation of the superior cervical ganglion.

At autopsy the complete division of the spinal cord at the fourth thoracic level and complete section of the right vago-sympathetic trunk were verified.

As a control experiment, to demonstrate that an identical stimulus applied to the superior cervical ganglion is ineffective in causing the reappearance of glucose in the urine, provided the animal be not permitted to reaccumulate glycogen by feeding, the following is included:

PROTOCOL XXIX. *Preliminary cord transection, with glycosuria: subsequent stimulation of superior cervical ganglion, without glycosuria, as no available glycogen.*

Previous to beginning the experiment the animal, a female cat, was confined and well fed for two days. At no time was there glycosuria.

December 20, 1911, 11 a.m. Etherization begun.

11.15. Urine on catheterization negative for sugar by Fehling's test.

12 m. Laminectomy, with complete transverse section of spinal cord at fourth thoracic level.

12.15 p.m. Catheterization unsuccessful.

2.45 p.m. Urine obtained by catheter strongly reduced Fehling's solution.

5 p.m. Catheterization unsuccessful.

December 21, 9 a.m. Urine by catheter (50 cc.) caused no reduction of Fehling's solution.

9.45 a.m. Etherization begun.

10 a.m. Vago-sympathetic trunk divided in middle of neck. Dissection of superior cervical ganglion. Faradic stimulation (coil at 8 cm.) applied to ganglion intermittently for fifteen minutes. Ether stopped at 10.15.

10.30 a.m. Catheterization yielded 10 cc. of urine, negative for sugar by Fehling's solution.

5 p.m. Catheterization unsuccessful.

December 22, 9.45 a.m. Under ether anæsthesia the abdominal wall was opened in the mid-ventral line. Bladder aspirated and emptied: 50 cc. of urine obtained; negative for sugar by Fehling's

<sup>7</sup> Macleod. Amer. Jour. Physiol., 1908, xxii, 373; Macleod and Ruh. *Ibid.*, 1911, 397; Macleod and Pierce. *Ibid.*, 1911, xxviii, 403; 1912, xxix, 419.



solution. Hepatic nerves in gastro-hepatic ligament dissected out and sectioned. Faradic stimulation (coil at 8 cm.) applied to ligament on hepatic side of area of section.

10.40 a.m. Abdominal wound closed.

2 p.m. Animal sacrificed.

At autopsy the section of the spinal cord at the level of the fourth thoracic nerves was verified. Urine in bladder (5 cc.) gave no reduction of Fehling's solution.

A comparison of the protocols of these two animals, which were subjected to identical conditions, leads one to the conclusion that the feeding resorted to in the first animal made possible the second mellituria from excitation of the superior cervical ganglion. In the second animal, after failure to elicit glycosuria from the ganglion stimulation, the several procedures about the gastro-hepatic ligament (any one of which would be certain in a glycogen-containing animal to evoke a tremendous glycosuria) were employed, demonstrating, by a sugar-free specimen of urine, that the animal had at the time no glycogen available for discharge.

The first of these two experiments is particularly significant, inasmuch as glycosuria was produced by excitation of the superior cervical ganglion after division not only of the homolateral vago-sympathetic trunk in the neck, but also of the spinal cord above the level of the splanchnic fibers. The only possible pathway for the impulse to travel, if we are dealing here with a purely nervous reflex to the liver, would be downward along the contralateral vagus. That the pathway is not caudalwards along the contralateral truncus sympathicus we have already shown.

(c) *After Spinal Cord Transection and Division of Both Vago-Sympathetic Trunks.*—It would seem that the likelihood of contralateral vagus conduction must be remote, for the vagus will probably be found to inhibit rather than induce glycogenolysis in the liver. However, to eliminate this possibility a cat's spinal cord was divided above the splanchnics, the animal was fed until it was believed that glycogen had reaccumulated, and then the vago-sympathetic cords were sectioned on both sides of the neck. Subsequent stimulation of the superior cervical ganglion gave rise to a very marked glycosuria.

*Protocol XXXIII. Preliminary spinal cord transection, with glycosuria; reaccumulation of glycogen. Stimulation of superior cervical ganglion, with glycosuria after division of both vago-sympathetic trunks.*

Previous to the beginning of the experiment the animal, a full-grown cat, was fed in its cage on a very liberal diet. All specimens of urine were sugar free.

March 25, 1912, 2.15 p.m. Etherization begun.

2.30 p.m. Laminectomy with division of spinal cord at the fourth thoracic segment.

2.40 p.m. Operation completed. Urine by catheter reduced Fehling's solution very strongly.

5 p.m. Urine by catheter gave marked reduction of Fehling's.

March 26, 10.45 a.m. Urine by catheter (30 cc.) negative for sugar by Fehling's and Nylander's tests.

11.15 a.m. Animal given by stomach tube 100 cc. of milk, at 37° C., containing a small amount of saccharose.

2 p.m. Urine by catheter gave no reduction of Fehling's solution.

2.15 p.m. Animal given by stomach tube 100 cc. of milk at 37° C., containing a small amount of saccharose.

5 p.m. Urine gave no reduction of Fehling's solution.

5.10 p.m. Etherization begun.

5.15 p.m. Section of left vago-sympathetic trunk in middle of neck.

5.18 p.m. Section of right vago-sympathetic trunk in middle of neck.

5.25 p.m. Exposure of right superior cervical ganglion.

5.28 p.m. Faradic stimulation (coil at 8 cm.) of right superior cervical ganglion for 30 seconds.

5.32 p.m. Similar stimulation for 30 seconds.

5.33 p.m. Etherization ended: closure begun.

5.38 p.m. Closure completed.

5.48 p.m. Urine obtained by catheterization gave extreme reduction of Fehling's and Nylander's solutions.

March 27, 10 a.m. Urine by catheter (18 cc.) gave a marked reduction by Fehling's and Nylander's solutions. Gravimetric determination showed 2 per cent monosaccharide content.

11 a.m. Animal sacrificed.

At autopsy the complete division of the spinal cord at the level of the fourth thoracic nerves and the two vago-sympathetic cords was verified.

Such an experiment—but one of a series of confirmatory observations—conclusively demonstrates that in the glycosurias resultant from stimulation of the superior cervical ganglion we are dealing not with a nervous reflex, but with a chemical stimulus to glycogenolysis arising somewhere in the cephalic course of the cervical sympathetic fibers. Observations similar to the one just quoted have been made on many cats and rabbits with uniformly positive results.

Though a corresponding experiment has not been made on the dog, nevertheless the glycosurias which occur in this species after section of the spinal cord, as well as after stimulation of the superior cervical ganglion, lead to the presumption that in these animals likewise the cervical sympathetic system is concerned in sugar metabolism in a way heretofore unappreciated, completely independent of a reflex arc which connects with its final relay in the splanchnic fibers.

In this group of experiments, as should be observed, all the nerves leading to any of the thoracic or abdominal viscera were divided before the final stimulus was applied to the superior cervical ganglion—that is, with the exception of the phrenic nerve; but it is inconceivable that we are dealing with a glycogenolysis excited by impulses which travel along this nerve.

(f) *With Open Synapses After Administration of Nicotine.*—Still further proof of the chemical nature of the impulse liberated ultimately by stimulation of the superior cervical ganglion is furnished by experiments with nicotinized animals in which the drug was given intravenously in amounts sufficient to open with certainty the synapses of the sympathetic system. Langley<sup>8</sup> has made use of 5 cc. of a 1 per cent solution of nicotine, given in this manner, to break the synaptic connections, but for absolute surety we have used larger amounts for dogs and proportionately larger amounts for cats.

<sup>8</sup> Langley and Dickinson: Proc. Roy. Soc., 1889, xlv, 423. Also: The action of various poisons upon nerve fibers. Jour. Physiol., 1890, xi, 509. Also: Pituri and Nicotin: *Ibid.*, 265.

The administration of nicotine intravenously calls for the maintenance of artificial respiration, for almost immediately after injection of the drug there ensues a hyperpnea and polypnea of extreme degree, followed in a few seconds by total apnea necessitating artificial respiration.

Our purpose in applying Langley's method was to assure ourselves that any glycosuria evoked by excitation of the superior cervical ganglion was the result of glycogenolysis inaugurated by the liberation of a chemical body and not of a neurogenic glycogenolysis through some unknown reflex arc somewhere in the organism. Hence, in these nicotinized animals, very soon after the presumed separation of the synapses the spinal cord was divided at a level with the fourth thoracic nerves. This procedure should elicit a prompt glycosuria if the stimulus need traverse no synapse to reach its final point of activity. In every case this procedure failed to cause a glycosuria.

Following this demonstration that section of the spinal cord is an ineffectual glycogenolytic stimulus in a nicotinized animal, stimulation of the superior cervical ganglion was resorted to, and this was quickly followed by an outpouring of large amounts of sugar into the urine—a definite argument in favor of the view that the stimulus from the superior cervical ganglion is independent of any essential synapse and leads to the discharge of a chemical substance producing glycogenolysis.

The experiment was first carried out on the cat, and it was found that after the preliminary tracheotomy under ether, the injection of the nicotine in itself maintained a complete anesthesia.\* In three successive experiments the results corresponded—no glycosuria from spinal cord section, glycosuria from stimulation of the superior cervical ganglion. The same procedure applied to a dog was followed by identical reactions. The data of this experiment follow:

*PROTOCOL LXXIV. Spinal cord transection in a nicotinized animal: no glycosuria. Stimulation of superior cervical ganglion: prompt glycosuria.*

Previous to the experiment the animal, an adult male dog, had been kept in a cage for fourteen days. By stimulation of the sciatic nerve glycosuria had been produced nine days previously. For eight days before the experiment the urine on daily tests was sugar free. The animal was in good condition and was affected in no appreciable way by the previous stimulation.

August 21, 1912. Urine under cage (170 cc.) negative for sugar by Fehling's and Nylander's solutions. Specific gravity, 1032.

10.32 a.m. Etherization begun. Tracheal tube inserted and right external jugular vein exposed. Complete evacuation of bladder.

10.45 a.m. Injection of 8 cc. of 1 per cent solution of nicotine (Merck) was made into the right jugular vein. Artificial respiration (bellows) was commenced, and was maintained until the end of the experiment. Administration of ether stopped just before the nicotine solution was administered.

\*As originally devised, the experiment was attempted on animals to which, instead of ether, chloroform was given in alcoholic solution as an anesthetic. We were unable to elicit glycosuria in these animals by any available method—even by the administration of large intravenous doses of adrenalin.

11 a.m. Laminectomy and complete transection of the spinal cord at the level of the fourth thoracic nerves.

1.15 p.m. Evacuation of bladder by abdominal pressure: urine (18 cc.) negative for sugar by Fehling's and Nylander's tests.

1.20 p.m. Exposure of right superior cervical ganglion. Faradic stimulation (coil at 8 cm.) was applied to the ganglion for three intervals of thirty seconds each, with intermissions of the same period.

3.50 p.m. Urine (22 cc.) obtained by abdominal pressure gave marked reduction of Fehling's and Nylander's solutions. Nicotine was still effective in opening synapses, as proved by failure to evoke pupillary dilatation on stimulation of the cervical sympathetic cord on the left side. Animal sacrificed.

These results appear to present definite proof that the melliturias with which we have been dealing are not of neurogenic character throughout. That the nicotine was given in sufficient amount in these experiments was evidenced by the failure in all cases to elicit glycosuria by spinal cord transection and by the fact that at the conclusion of the experiments stimulation of the sympathetic trunk in the neck resulted in no pupillary dilatation—both phenomena being dependent on the integrity of the synapses. The impulse, then, aroused by stimulation of the superior cervical ganglion must necessarily have been such that it passed through no synapses before discharging the store of glycogen or liberating the chemical messenger which caused the glycogenolysis. The latter alternative is, of course, by far the more likely.

(g) *After Extirpation of the Posterior Lobe of the Hypophysis.*—Proof that a chemical substance plays the essential rôle in the melliturias following stimulation of the superior cervical ganglion would of course be obtained if some organ capable of giving rise to such a substance were to be excised and subsequent ganglionic stimulation fail to produce glycosuria. We have found that glycosuria does not appear after the customary ganglionic stimulation in dogs in whom the pars nervosa of the hypophysis has previously been removed. We have used four dogs for this test, and in all of them we have failed to elicit the customary glycogenolytic response to the excitations. A typical protocol follows:

*PROTOCOL XLVII. Stimulation of the superior cervical ganglion after extirpation of the posterior lobe of the hypophysis: no glycosuria.*

The posterior lobe of the hypophysis having been removed from an adult male dog eight weeks previously (i.e. February 15; Jacobson's series, No. 12), the animal was fed bountifully for a week before stimulation, and for the three antecedent days, in order to assure the presence of available glycogen, an aqueous sugar solution was given by stomach tube (saccharose, grams 40) twice daily. At no time did sugar appear in the urine.

April 25, 1912. Urine obtained just previous to operation possessed no reducing bodies (Fehling's and Nylander's solutions).

11 a.m. Etherization begun.

11.20 a.m. Exposure of superior cervical ganglion on the left side. Faradic stimulation (coil at 6 cm.) applied to ganglion for three intervals of thirty seconds each with intermissions of the same period.

11.30 a.m. Closure completed.

5 p.m. No urine under cage.

April 26, 9 a.m. No urine under cage.

5 p.m. No spontaneous micturition, so animal given a whiff of ether, and 250 cc. of urine obtained by abdominal pressure. No reduction of Fehling's and Nylander's solutions. Specific gravity 1.050.

April 27, 9 a.m. Urine under cage, 105 cc. Specific gravity 1.042. Negative for sugar.

The uniformity of the results in other experiments of this type gives further support to the view that stimulation of the superior cervical ganglion causes a discharge into the blood stream of the posterior lobe secretion.<sup>10</sup> Whatever may be the nature of the chemical substance thus discharged, it is presumably carried through the vascular system to the glycogen storehouses of the body, either in the liver or in the muscles, where it inaugurates glycogenolysis. The exact method by which this liberation of glycogen as dextrose into the circulation is brought about is conjectural: the hypophysial substance may act as the necessary hormone; it may stimulate nerve terminals to liberate glycogenase; it may activate the glycogenase.

#### 4. EFFECTS OF DIRECT STIMULATION OF THE HYPOPHYSIS.

We had long been aware that certain manipulations of the gland during the performance of a canine hypophysectomy would evoke glycosuria, and the hypophysial piqûres mentioned in this paper were supposed to occasion a similar mechanical discharge of the secretion. Having shown that a discharge of the active principle, as evidenced by a succeeding glycosuria, would follow the electrical stimulation of a superior cervical ganglion when severed from all connections except its post-ganglionic fibers, we were led, as a next step, to faradize the gland itself.

Our observations in this direction have been made both upon the cat and dog, in which animals the hypophysis may be easily exposed by a transphenoidal route through the mouth. Female cats were preferred, as they were more susceptible to catheterization. Ether was given, but in an amount insufficient to cause a complicating glycosuria from the drug. The animals were catheterized immediately after the onset of surgical anesthesia, and after the hypophysis was exposed a second sample of urine was taken, as a precaution against the possibility of the operative trauma evoking glycosuria. In none of these animals was sugar found in the urine in either specimen. After a faradic stimulation was applied to the hy-

<sup>10</sup> It should be noted that after any operative removal of the pars nervosa some of the pars intermedia may still remain in contact with the ventricular stump of the hypophysial stalk, along which the nerves course to the gland. Under these circumstances it might be assumed that the stimulus applied to the superior cervical ganglion could still serve to discharge sufficient hyaline substance to evoke glycosuria. Hence, in this group of experiments, even had a slight glycosuria occurred after the ganglion stimulation, our conclusions need not have been modified. As it was, the absence of glycosuria in these animals, in view of their having been well fed and confined to cages for at least a month before the ganglion stimulation, is the more striking, and offers additional, though negative, proof that stimulation of the superior cervical ganglion results in a glycosuria having its chemical origin in the hypophysis.

pophysis, however, a marked glycosuria in most cases promptly occurred. The record of a typical experiment follows:

PROTOCOL LXXVII. *Direct faradic stimulation of the hypophysis, with prolonged glycosuria.*

December 25, 1911. Female cat. 10.05 a.m. Etherization begun. Urine (10 cc.) negative for sugar by Fehling's and Nylander's reactions.

10.07-10.50 a.m. Exposure of hypophysis by buccal route.

10.53 a.m. Urine (5 cc.) negative for sugar by Fehling's and Nylander's tests.

10.54 a.m. Faradic stimulation of gland for two minutes. Ether removed. Prompt recovery.

12.10 p.m. Urine (10 cc.) strongly reduces Fehling's and Nylander's solutions.

December 26, 9 a.m. Urine voided during night (55 cc.) showed abundant sugar (Fehling and Nylander).

December 27, 9 a.m. Urine (20 cc.) negative for sugar (Fehling and Nylander).

December 28 and 29. Urine remained negative for sugar by all tests.

This experiment indicates that direct faradic stimulation of the hypophysis is capable of causing a marked glycosuria, prompt in appearance and enduring for some hours. That this glycosuria cannot be attributed to the mere operative trauma incidental to the transphenoidal approach is well shown by the following experiment, in which, owing to surgical difficulties, an incomplete denudation of the gland was made at the first operation, no glycosuria resulting even after faradic stimulation of the neighborhood. At a subsequent operative session the gland was fully exposed and glycosuria promptly followed the stimulation. This was repeated on five successive occasions, a sufficient interval for the reaccumulation of glycogen being allowed between the stimulations.

PROTOCOL LXXIX. *Incomplete denudation of hypophysis with faradization: no glycosuria. Subsequent complete exposure, with faradization and glycosuria, repeated on five occasions, with intervals for glycogen reaccumulation.*

January 10, 1912, 10.10 a.m. Female cat anesthetized.

10.13 a.m. Catheter specimen of urine (10 cc.) negative for sugar by Fehling's and Nylander's tests.

10.15 a.m. Small transphenoidal opening in base of sella with incomplete exposure of gland: difficult operation.

10.53 a.m. Catheter specimen (11 cc.) negative (Fehling and Nylander).

10.54 a.m. Faradic stimulation with electrodes at bottom of sphenoidal wound for two minutes.

1 p.m. Catheter specimen (8 cc.) negative for sugar (Fehling and Nylander).

January 11, 12 and 13. Urine voided on each of these days remained sugar free.

January 14, 9 a.m. Urine voided (30 cc.) negative for sugar (Fehling and Nylander).

10.20 a.m. Ether anesthesia. With a more complete removal of bone from the sellar base the hypophysis was fully exposed.

11.05 a.m. Urine by catheter (8 cc.) negative for sugar (Fehling and Nylander).

11.08 a.m. Faradic stimulation of gland for three minutes.

January 15, 9 a.m. Urine obtained since stimulation (15 cc.) showed abundant sugar by Fehling's and Nylander's tests.

January 16 to 21 inc. Urine voided on each of these days negative for sugar (Fehling and Nylander).

January 22. Morning urine (15 cc.) negative for sugar by Fehling's and Nylander's solutions.



Under ether anaesthesia the hypophysis was again exposed and faradic stimulation applied to the gland for three minutes; duration of anaesthesia twenty minutes. Urine (4 cc.) obtained by catheter just before stimulation negative for sugar (Fehling and Nylander).

Urine (7 cc.) by catheter fifteen minutes after stimulation showed abundant sugar by Fehling's and Nylander's solutions.

January 23, 9 a.m. Urine voided since operation (25 cc.) showed abundant sugar by Fehling's and Nylander's tests: gravimetrically, 5 per cent sugar.

January 24 to February 6 inc. Animal fed on routine laboratory diet for these two weeks. Urine remained sugar free.

February 7. Fourth exposure and stimulation of hypophysis. Urine (18 cc.) obtained by catheter at the beginning of ether anaesthesia, and also (4 cc.) just before the stimulation was begun, negative (Fehling and Nylander) for sugar. Faradic stimulation applied to the gland for three minutes. Duration of ether anaesthesia, twenty minutes. Urine voided during the following night (25 cc.) showed abundant reduction of Fehling's and Nylander's solutions.

February 8 to 12 inc. Urine remained sugar free on these days, the animal being fed on routine laboratory diet.

February 13. Fifth exposure and faradic stimulation (three minutes) of hypophysis, followed by a marked glycosuria.

February 14 to March 6 inc. Urine remained sugar free.

March 7. Sixth exposure and faradic stimulation of hypophysis, as on the previous occasion. A prompt glycosuria of 4 per cent sugar content in urine followed.

The foregoing protocol clearly indicates that direct faradic stimulation of the pituitary body, with an intact nervous system, will incite mellituria. This, as well as our preceding experiences, had begun to make us reasonably certain that the gland, and probably the pars nervosa, under the proper stimulus liberates a chemical substance capable of inducing glycogenolysis. Others have expressed the view that there exists a "diabetic center" in the tuber cinereum, and that this, rather than the pituitary body, accounts for the glycosurias which our predecessors observed in the earlier experiments reported from the Hunterian Laboratory. Hence, to make the foregoing experiment still more conclusive, it was necessary to eliminate, by a spinal cord transection, the possibility that our stimulus might have acted on some center in the cerebro-spinal axis capable of eliciting a purely neurogenic mellituria.

It was found that glycosuria may be evoked by direct stimulation of the gland substance even after division of the spinal cord above the splanchnic outflow, provided opportunity be allowed for the reaccumulation of glycogen necessarily discharged by this procedure (*cf.* appendix). In this series of experiments it was not considered necessary to section the vagi and the sympathetic trunks in the neck, as our earlier observations on the melliturias inaugurated by stimulation of the superior cervical ganglion showed that impulses capable of eliciting glycogenolysis did not descend by way of these nerves. The record of one of these experiments will suffice.

PROTOCOL LXXII. Preliminary transphenoidal exposure of hypophysis, with glycosuria. Transection of spinal cord, with glycosuria. Reaccumulation of glycogen. Direct stimulation of hypophysis with resultant glycosuria.

August 1, 1912. Adult female cat. 11.20 a.m. Etherization begun.

11.25 a.m. Catheterization: 16 cc. of sugar free urine obtained.

11.30 a.m. Exposure of hypophysis by buccal route begun.

11.40 a.m. Operation completed: a quick, uncomplicated procedure, giving a good view of both lobes of the gland. Urine by catheter (8 cc.) negative for sugar by Fehling's test.

11.45 a.m. Faradic stimulation (coil at 6 cm.) of hypophysis; for three intervals of thirty seconds each, with intermissions of the same period.

11.55 a.m. Closure of soft palate completed.

August 2, 9 a.m. No urine voided. A specimen obtained by abdominal pressure (50 cc.) caused marked reduction of Fehling's solution. Gravimetrically, 2.5 per cent sugar.

August 3, 9 a.m. Urine under cage (65 cc.) caused no reduction of Fehling's solution.

August 4 to 9 inc. Urine sugar free. Routine feeding in cage.

August 10, 9 a.m. Urine under cage (50 cc.) caused no reduction of Fehling's or Nylander's solution.

10 a.m. Etherization started. Laminectomy and transection of spinal cord at fourth thoracic segment. Wound closure completed at 10.30.

August 11, 10 a.m. Bladder emptied by abdominal pressure. Urine (45 cc.) reduced Fehling's and Nylander's solutions. Animal then given 50 cc. of warmed milk by stomach tube.

August 12, 9 a.m. Urine by abdominal pressure (48 cc.) negative for reducing bodies by Fehling's and Nylander's solutions. Given 50 cc. of warmed milk by stomach tube.

3.30 p.m. Urine by abdominal pressure (18 cc.) negative for sugar. Given 50 cc. of warmed milk, containing 2 grams of saccharose, by stomach tube.

August 13, 9 a.m. Urine by abdominal pressure (52 cc.) gave no reduction of Fehling's or Nylander's solution. Given 50 cc. of warmed milk, containing 3 grams of dextrose.

2.30 p.m. Urine by abdominal pressure (12 cc.) negative for sugar.

2.45 p.m. Re-exposure of hypophysis through original pathway. Faradic stimulation of the gland (coil at 8 cm.) for two intervals of forty-five seconds each with an intermission of thirty seconds. After stimulation the posterior lobe of the gland, with a small portion of the anterior lobe, was excised.

3.15 p.m. Etherization ended. Reclosure of palate completed.

August 15, 9 a.m. Urine obtained by abdominal pressure (34 cc.) showed a marked reduction of Fehling's and Nylander's solutions. Animal in good condition. Given 50 cc. of milk at 37° C.

5 p.m. Urine by abdominal pressure (16 cc.) still reduced Fehling's and Nylander's solutions. Animal given 50 cc. of milk at 37° C.

On August 16 the urine became sugar free and remained so. The animal was given milk by stomach tube for four days—a sufficient time for the reaccumulation of glycogen—and an attempt was then made to stimulate the superior cervical ganglion, with the expectation that, as in other experiments of the kind, no mellituria would be evoked, owing to the posterior lobe extirpation of August 13. The animal died under the anaesthetic soon after the exposure of the ganglion.

At autopsy the complete transverse division of the spinal cord and the opening into the sella turcica, with extirpation of the posterior lobe, were verified.

The foregoing record indicates that direct stimulation of the hypophysis evokes glycogenolysis and glycosuria through a chemical messenger rather than by any nervous mechanism connecting the encephalon with the abdominal viscera."

"As will be observed, we have employed, as the basis of these experiments, the discharge or otherwise from the gland of the substance capable of producing glycogenolysis. The gland doubtless contains other substances or hormones, or else this same substance is capable of eliciting other reactions—notably those of a hæmodynamic nature.

In a single experiment we endeavored to obtain the record of a hæmodynamic response to direct glandular faradization, but no change in carotid pressure occurred during the interval of stimulation. This matter calls for further investigation; for it seems not unlikely that a considerable period of time must elapse before the secretion of the pars nervosa enters the circulation, particularly if, as we believe to be the case, it reaches the blood stream through the intermediation of the cerebrospinal fluid. Under these circumstances no hæmodynamic evidence of hypophysial discharge need be expected in a carotid tracing until some minutes after the initial stimulus, and the same is true of the glycogenolytic hormone, for this substance doubtless likewise takes the same route to the blood stream.

We are in need of chemical reactions to detect small quantities of these substances in the blood, such as Folin has given us for adrenalin; but it will first be necessary to determine the chemical composition of the active principle and possibly to synthesize it before satisfactory test reactions can be expected.

### 5. BULBAR PIQÜRES AFTER SPINAL CORD TRANSECTION.

As during the progress of these studies our premise of a nervous impulse passing from the bulb by way of the cervical sympathetic and presiding over the secretory activity of the posterior lobe of the pituitary body received further support, many collateral experiments were made, which need not be detailed here, as they do not add essentially to the strength of the argument.

There is but one further step which may deserve mention; and this brings us back to the original piqûre of Bernard in the rabbit which heretofore has been thought to provoke hepatic glycogenolysis solely through an autonomic mechanism involving splanchnic nerves and adrenal glands.

It seemed reasonable to expect that a typical bulbar piqûre in a nicotineized animal would fail to produce glycosuria, owing to the opened synapses throughout the autonomic system; whereas stimulation of the pituitary body itself should not fail to give sugar even in an animal under the full influence of this drug. Furthermore, in view of our experiences with spinal cord transection and reaccumulation of glycogen, the possibility of producing glycosuria by a bulbar piqûre through the intermediation of the hypophysis, after such a transection above the splanchnics, naturally suggested itself.

The nicotine experiments in the rabbit were unsuccessful, as the animals invariably succumbed to such a dosage as we thought necessary to insure opening of the synapses. Hence the negative bulbar piqûre under these circumstances remains a matter of presumption. Positive results, however, were obtained by piqûres in the animals after spinal cord transection.

Observations were made on four normal rabbits. After the spinal transection at the fourth thoracic level, they were allowed to feed, in preparation for the subsequent medullary piqûre, until it was believed that glycogen had reaccumulated. The piqûres were made through the cerebellum into the rhombencephalon, after the method of Dandy and Fitzsimmons. Three of the animals were subjected to identical experimental conditions: in two of them the piqûre evoked a marked glycosuria. The data of one of the experiments follow:

PROTOCOL XLVIII. *Transection of spinal cord at T. IV: subsequent Bernard piqûre, with glycosuria.*

April 22, 1912. Adult male rabbit. 11 a.m. Urine obtained by catheter: no reduction of Fehling's or Nylander's solution.

12 m. Laminectomy: spinal cord sectioned at the fourth thoracic level. Wound closed at 12.30. Prompt recovery, with resumption of feeding.

4 p.m. Urine obtained by catheter (30 cc.) reduced Fehling's and Nylander's solutions. Animal given raw apple.

April 23, 9 a.m. In good condition. Urine on catheterization (115 cc.) negative for sugar by Fehling's and Nylander's solutions.

10.50 a.m. Trephine opening for medullary piqûre.

11 a.m. Piqûre wire inserted in usual manner.

12 m. Urine by catheter (23 cc.) strongly reduced Fehling's and Nylander's solutions. Gravimetrically, 1.25 per cent of monosaccharide; by polarization, dextro 1.2 per cent.

1.45 p.m. Urine obtained by catheter (20 cc.) caused marked reduction of Fehling's and Nylander's solutions. Gravimetrically 4 per cent sugar.

4 p.m. Animal sacrificed. Urine in bladder (16 cc.) caused marked reduction of Fehling's and Nylander's solutions. Section of spinal cord found to be complete at the level of fourth thoracic nerves. Typical bulbar piqûre.

Such an observation indicates that the impulse from a Bernard medullary piqûre, in addition to its well-known effect on the adrenals, serves to discharge a glycogenolytic substance from some other gland of internal secretion—obviously in this case the pituitary body. To be sure, the vagus and sympathetic trunks had not been divided, but our earlier experiments have excluded the possibility of the vagus playing a functional rôle in these cervical glycosurias.

In the third of the three experiments carried out under identical surgical circumstances the Bernard piqûre failed to evoke a glycosuria. However, on subsequent stimulation of the superior cervical ganglion sugar promptly appeared in the urine, showing that there was available glycogen, and justifying the conclusion, in view of the two other experiments, that the piqûre had been faulty.

We used the fourth rabbit of this series to tell whether the medullary piqûre would cause glycosuria if performed after section of the two sympathetic trunks in the neck in addition to the cord transection; for a positive result would indicate that some impulse could reach the gland other than by way of the known cervical pre-ganglionic fibers. The piqûre actually gave glycosuria; but no definite conclusions are permissible, owing to the finding at autopsy of an additional fiber bundle—not a part of the vagus—which lay in the carotid sheath and which had not been sectioned; this in all probability was a detached filament of the cervical sympathetic cord. We have had no opportunity to repeat the procedure, and merely record the observation here as being suggestive.<sup>12</sup>

<sup>12</sup> It is of interest to recall the early views of Bernard and Eckhard in regard to the emergence of splanchnic fibers in the three upper thoracic nerves. Eckhard in particular (*Die Stellung der Nerven beim künstlichen Diabetes*. Beitr. z. Anat. u. Physiol. 1869, iv, 3-32) supported the conception that the typical bulbar piqûre elicited glycosuria by splanchnic excitation, the specific glycogenolytic fibers supposedly leaving the upper cord. It would seem that these earlier observers erred in assuming a downward

Though the experiments in this particular group are few, with the evidence in hand we feel justified in stating that a medullary piqure, after division of the spinal cord above the level of the splanchnics, will cause glycosuria, evidently by the discharge of some chemical substance which evokes glycogenolysis; and that the hypophysis furnishes this substance seems by far the most likely explanation.

From the results of the experiments which have been cited in this paper it is fair to assume the existence of a nervous control on the part of the sympathetic system over one form at least of the secretory activities of the pituitary body. The particular function of the gland—and presumably of its posterior lobe—on which our studies have been based concerns the elaboration and discharge of a substance capable of evoking glycogenolysis.

Doubtless other of the so-called ductless glands operate under a similar autonomic influence, and in the case of the adrenal this has been particularly well brought out by Macleod and his collaborators. However, owing to the comparative ease with which the post-ganglionic fibers which reach the pituitary gland may be experimentally isolated from the rest of the nervous system, this member of the ductless gland series would seem to offer a better opportunity for the demonstration of a clearly chemical glycosuria occasioned by the discharge of an internal secretion than does even the adrenal.

It remains to be shown, in the first place, just how the functional<sup>12</sup> or pathological glycosurias originating from disorders of the hypophysis actually occur, whether from some unusual and continued neurogenic influence, from an external chemical stimulus, or from an actual increase, through glandular hyperplasia, of the normal secretory output: in the second place, how the glandular secretion actually serves to evoke the glycogenolysis, whether it acts on nerve endings in the hepatic and muscular storehouses of glycogen, or whether it liberates and transforms glycogen by a direct chemical interaction within the cell.

However these things may be, certainly in the future the discharge of a chemical messenger from the hypophysis will have to be taken into account when considering the encephalic glycosurias, whether of purely emotional or of pathological origin. It may be noted in closing, moreover, that heretofore the relation of the glands of internal secretion to the sympathetic system proper, alone, has been made the particular

course for the fibers which leave the cerebrospinal axis in the first three thoracic nerves. The glycosurias which they obtained were undoubtedly of the same origin as those with which this paper deals. The later work of Langley has definitely limited the superior origin of the splanchnic nerves to the fifth and very rarely to the fourth thoracic nerves. Hence the impulse aroused in the first three thoracic nerves must travel upward in order to elicit the ensuing glycosuria, and not downward as in the splanchnic collection.

<sup>12</sup> It has been suggested that the glycosurias of adolescence, as well as those of pregnancy and other physiological states, are largely influenced by coincident hypophysial changes. (*The Pituitary Body and Its Disorders*. 1912. J. B. Lippincott Company).

object of study. Doubtless in time their equally important relation to the craniosacral system will be investigated and studies made to determine the impulses which inhibit secretion.

## 6. SUMMARY.

Provided there is a storage of glycogen available for discharge:

1. A piqure of the hypophysis in the rabbit is comparable, in its glycosuric response, to a piqure of Bernard's so-called sugar center in the fourth ventricle.
2. Stimulation of the superior cervical ganglion, by faradization or even by the manipulations necessary for its exposure, causes glycosuria in the rabbit, cat and dog.
3. Stimulation of the superior cervical ganglion after exclusion of all possible downward impulses to the abdominal viscera by way of the vagi, cervical sympathetic trunks, or spinal cord, leads to glycosuria.
4. Stimulation of the superior cervical ganglion after separation of all synapses of the sympathetic system by administration of nicotine, causes glycosuria.
5. Direct faradic stimulation of the hypophysis itself, after exposure by a transphenoidal operation, gives glycosuria even after preliminary transection of the spinal cord and cervical sympathetic trunks.
6. If the posterior lobe of the hypophysis has previously been removed by operation the usual stimulation of the superior cervical ganglion fails to give glycosuria.
7. Direct faradic stimulation of the hypophysis provokes glycosuria even after transection of the spinal cord above the splanchnics.
8. A Bernard piqure will likewise cause glycosuria even after transection of the spinal cord above the splanchnics.

## 7. CONCLUSIONS.

The pituitary body, and more particularly its posterior lobe, plays a significant rôle in the metabolism of carbohydrates, and its action in this respect is under the control of fibers which reach the gland by way of the superior cervical sympathetic ganglion. Stimulation of this nervous pathway at the so-called sugar center in the fourth ventricle, at the superior cervical ganglion, and by excitation of the pituitary body itself, liberates a chemical substance which causes glycogenolysis and glycosuria, independent of any possible nervous impulse reaching the glycogen-holding cells of the muscles or abdominal viscera.

## APPENDIX.

### *The Significance of Available Glycogen.*

Throughout the foregoing pages frequent use has been made of the term "*available glycogen*" when explaining the occurrence or otherwise of glycosuria in an animal subjected to a given stimulus. We feel the necessity of explaining at some length our position in regard to the glycogen content of the body, in view of the importance of the subject in all experimental studies of glycosuria.

Bernard, in his original description of the glycosuria incited



by a medullary puncture, found that sugar did not appear in the urine of animals which had been previously deprived of food. Naturally, under these circumstances, the starvation led to a decrease in the carbohydrate content of the liver. The store of glycogen may be exhausted under other conditions—in strychnine poisoning, for example; for if the drug is given in amounts sufficient to cause convulsions not enough glycogen remains to be discharged by the ordinary methods of eliciting glycosuria.

An essential factor in our experiments was the production, by a second excitation, of another wave of hyperglycemia and glycosuria after the animal's urine had become sugar free. It was observed that the initial period of glycosuria, after one or another of the potent stimuli—for example, after spinal cord transection—was surprisingly short, showing either that the effect of the excitation was transient or else that the stimulus discharged but little of the glycogen held by the body. Moreover, some histological studies were made of the glycogen content of the liver cells after staining with Best's carmine, and it was seen that there was an abundant glycogen residual in many of the cells even after a copious glycosuria had followed an antecedent stimulus.

Hence we anticipated that a further discharge of glycogen could be brought about by the repetition of some known form of glycogenolytic excitation after the animal's urine had again become sugar free; but it was found that a second stimulus would rarely, if ever, evoke glycosuria unless the animal in the interval had been fed in such a manner as to encourage a further storage of glycogen.

A few of our experiences in this regard have been related in connection with some of the foregoing protocols, but it was largely the negative results which finally brought us to our present interpretation of the matter—namely, that there exists in the body a supply of glycogen in considerable amount shortly after feeding, but which diminishes rather rapidly. This supply of course does not include all of the glycogen of the body, not even the total glycogen content of the liver, but corresponds with what we have come to designate as "available glycogen."

The distinguishing features of this store of glycogen are, the readiness with which it may be discharged by the stimuli which we have used (Bernard piqûre, hypophyseal piqûre, stimulation of the superior cervical ganglion, cord division, section of the nerves to the liver, and direct stimulation of the hypophysis) and its failure to reaccumulate unless feeding be resorted to.

Our evidence in no way justifies the belief that, after application of one or another of the glycogenolytic stimuli, all of the glycogen of the body is exhausted—a phenomenon which may possibly occur after prolonged starvation or severe strychnine poisoning. Indeed we feel assured that this is not the case; for there seems to exist, in addition to the basic store of glycogen, a more unstable supply capable of being liberated or mobilized by a degree of stimulation which fails to influence the basic supply. In all likelihood the long continued application of our weaker excitations might ultimately have

resulted in the liberation of the basic or immobile glycogen, but of this we have no proof. We have therefore interpreted our results from the standpoint of this rather vague classification of the glycogen content of the body—the basic or difficult of discharge, and the mobile or available supply.

The question immediately arises as to whether animals always have an available glycogen content if their tissue carbohydrates have in no way been previously discharged. In the case of dogs we have found that stimulation of the superior cervical ganglion by a mild faradic current always results in glycosuria, provided the animal has been bountifully fed and has been confined in a cage for three or four days previous to the procedure: under these circumstances in no instance have we failed to elicit glycosuria. On the other hand, the application of the same excitation under similar conditions in the case of dogs which have been taken from the animal yard just before the observation seldom results in glycosuria. Such a phenomenon seems to indicate that the activities of the dog in the yard constantly form a demand upon the glycogen supply of the body, with the result that the weak excitation which we have used is ineffective when the more unstable transient "available glycogen" is thus exhausted.

The constancy with which glycosuria has followed excitation of the superior cervical ganglion in dogs confined to their cages for periods of over three days we feel is a very important factor in the argument that such a stimulation affects the *pars nervosa* of the hypophysis; for in every instance the animals in whom the posterior lobe had been extirpated failed to show glycosuria, though they had previously been in confinement and though practically all of them had a high sugar tolerance, assuring a plentiful glycogen supply.

Evidence favorable to this conception of glycogen storage is afforded by such an observation as the following. Stimulation of the superior cervical ganglion of a dog that had been allowed the freedom of the paddock failed to evoke glycosuria. The animal was then confined to his cage for some days on the same routine diet, when the ganglion on the opposite side was exposed and stimulated, with a resultant copious discharge of sugar—owing, we presumed, to the storage, betweenwhiles, of glycogen available for discharge.

Under the usual laboratory conditions the cat and rabbit apparently possess a more easily available store of glycogen than does the dog. These animals not only lead a quiet laboratory existence, but the diet also constitutes an important factor in the provision of an adequate content of mobile glycogen. For the cats, milk has been given, while the abundant carbohydrates in the vegetables fed to the rabbits assure large amounts of glycogen in these animals. Hence it does not seem at all strange that we should have found our weak stimuli effective in practically all cases in cats and rabbits, whereas with dogs the same excitations at times proved ineffective unless special care had been taken to insure inactivity and abundant feeding.

For these reasons, in our varied experiments failure to obtain glycosuria has been considered from the standpoint of available glycogen. If any procedure failed to provoke glyco-

suria, the subsequent demonstration of the presence or absence of mobilizable glycogen was considered necessary; and no result was considered reliable unless this check was made. The three procedures which we have employed for this purpose are (1) stimulation of the superior cervical ganglion; (2) division of the spinal cord, and (3) stimulation of the hepatic nerves in the gastro-hepatic ligament.

As our investigations chiefly concerned the relation of the superior cervical ganglion to the hypophysis, the negative results of ganglionic stimulation concerned us most. But in no case were we able to elicit glycosuria by either of the other two methods after a primary excitation of the ganglion had proved ineffective. The three procedures appear to be equally capable of causing a discharge of glycogen; and stimulation at any one of the three situations apparently results in the discharge of all available glycogen, if available glycogen be present.

#### SPINAL CORD TRANSECTION AND GLYCOSURIA.

In the course of these studies, in order to assure ourselves that the stimulation of the cervical sympathetic ganglion did not reach the abdominal viscera and act upon the adrenals or splanchnic system by the operation of some retrograde or "antidromic" (Bayliss) impulses which operated contrary to the Bell-Magendie law, we attempted to exclude this possibility by the preliminary transection of the spinal cord above the splanchnics. As might possibly have been expected, this procedure invariably provoked glycosuria provided there was available glycogen. As we are unfamiliar with any similar observations, the matter may deserve a word of comment.

It was found in the dog, cat or rabbit that the transection of the cord at any segment provoked glycosuria, though most of the divisions were made cephalad to the level of emergence of the splanchnics. The operation is simple and brief, and in our routine procedure, after the laminectomy a grooved director was passed beneath the cord and its enveloping meninges. A complete transverse section was assured by cutting down upon the director, and bleeding from the stumps was controlled, if necessary, by the application of small bits of raw muscle.

In dogs and cats ether was used, but in the case of rabbits local anæsthesia by infiltration methods, with cold water or cold salt solution, sufficed. Control observations were made, to eliminate the possibility that the glycosuria might be due to the anæsthetic. Cocaine was not employed as the local anæsthetic, on account of the likelihood of occasioning a glyco-

suria by sensitizing the terminals of the sympathetic fibers to the action of adrenalin.

One striking feature of the glycosuria provoked by spinal cord section is the promptness with which sugar makes its appearance. In many of our experiments catheterization was resorted to as soon as the operative wound was closed; and in many cases the glycosuria was demonstrable within ten minutes after the transection.

Another characteristic of these glycosurias is their short duration, for as a rule the urine becomes sugar free by the end of the first twenty-four hours, unless the sugar content of the food has exceeded the temporarily lowered carbohydrate assimilation limit or unless some further glycogenolytic stimulus has been superadded.

In the case of the rabbit no difficulty has been experienced in the question of feeding if it has been essential to the problem at hand to assure the reaccumulation of glycogen in order to test the effects of a subsequent stimulus; for these animals will usually resume their nibbling of the food placed before them immediately after the cord transection. In the few animals which have failed to do so, attempts to administer food artificially have been futile. After transection in the cat we have found it desirable to administer the milk by stomach tube, as indicated in the protocols which have been given.

By far the greater number of our cord transections have been made at the fourth thoracic segment, for at this level the division can be made caudad to the emergence of fibers into the cervical sympathetic cord and cephalad to the splanchnic outpouring. However, our few experiments with transection at other segments indicate that cord division at any level provokes mellituria provided the animal has a store of available glycogen.

In all likelihood the transection stimulates all the tracts in the cord, more especially the fibers going to the splanchnic nerves, and causes hepatic glycogenolysis through activation or liberation of glycogenase, as Macleod has shown. There is doubtless an increased outpouring of the active principle of the adrenals into the blood stream, and the response may be entirely in accord with the view that a Bernard medullary pigûre acts by adrenal stimulation. However, in view of the rôle played by the cervical sympathetic in the control of the pars nervosa, it seems not unlikely that spinal transection acts by sending forth a general excitation to all the glands of internal secretion, whose secretory discharge results in mellituria.

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## INDUCED PNEUMOTHORAX IN THE TREATMENT OF PULMONARY DISEASE.\*

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Rest has long been accepted as an important condition for the recovery of inflamed tissues. In many locations pain necessitates it and physicians exaggerate and prolong the remedial measure that nature suggests. Particularly in tuberculous infections has its enforcement given brilliant results, and numerous observations have led to the conclusion that rest is as valuable a remedy in pulmonary tuberculosis as in tuberculosis of other regions. Towards the end of the last century the frequent beneficial effects of pleural effusion upon tuberculous lesions in the lung arrested attention. The relation is often striking. Concomitantly with the appearance of fluid, fever abates, cough and sputum decrease, and the patient's general condition improves. Aspiration of the exudate may be followed by a recurrence of the previous symptoms, which again subside as the fluid reaccumulates. L. Spengler has published striking instances of this not uncommon occurrence. He suggests injecting silver nitrate into the pleural cavity to increase and prolong the effusion. Galliard writes of such effusions under the title *pleurésies providentielles*. Mosheim has collected many convincing observations from the literature. Konselman has made it the subject of an interesting study. The beneficial results are ascribed to the immobilization of the diseased lung.

One of the most dreaded complications of advancing tuberculosis of the lungs is the occurrence of pneumothorax. Coming as a rule at the end of a prolonged and wasting illness it usually marks the rapid approach of death. West, in 101 cases, found that in 75 per cent death occurred within fourteen days of the onset of pneumothorax. Drasche, in 198 cases, found a rate of 71 per cent. Brunicke, Grissolle, Valleix, and others regarded pneumothorax developing in the course of pulmonary tuberculosis as invariably fatal. Ruhle had never heard of a case ending in recovery with concomitant healing of the pulmonary lesion. Such instances, however, began shortly after to be recorded. At first isolated examples were published as medical curiosities, later the observations became more common. Of Drasche's 198 cases only one recovered completely. West reported 11 cured out of 167 instances. Mosheim considered that the tuberculous nature of some of West's cases was doubtful, and in a number of others the healing incomplete. He allowed only six definite recoveries; three without the appearance of pleural exudate, three with serous or sero-purulent exudate. In one of the six the pulmonary

tuberculosis healed concomitantly. Mosheim reported one recovery in 42 instances of pneumothorax occurring in pulmonary tuberculosis. A number of the cases showed marked immediate improvement. Rose observed three recoveries in nineteen instances. Only eight of Spengler's twenty cases died; seven were discharged unimproved; one case recovered and the pulmonary lesion healed, but a serous exudate remained; four cases completely recovered, and in three of these the pulmonary lesion likewise healed.

Pneumothorax in itself is a very benign condition. The rapidly widening experience with induced pneumothorax, as we shall later point out, attests this. In healthy individuals complete collapse of one lung may occasion but trifling symptoms and easily escape detection. We have observed two instances of spontaneous pneumothorax in otherwise healthy men associated only with slight dyspnea on exertion, and a transient stitch in the side. Bach, Goodhart, Hall, Jochman, Pepper, Sale, Weber, West and others report similar cases. The fatal effects of pneumothorax in pulmonary tuberculosis must then be ascribed to associated conditions. Usually it is but a terminal event in a patient worn by rapidly advancing disease, and already overshadowed by death; the almost constantly associated pleural infection adds an extensive area for septic absorption; and in many instances mechanical conditions at the point of rupture induce fatally high intrapleural pressure.

Occasionally, even in advanced tuberculosis, the advent of pneumothorax marks the beginning of improvement in the pulmonary condition. The symptoms of progressing disease abate, the patient's general condition improves, and the signs of pulmonary involvement diminish. Such an observation led Carson, in 1821, to propose inducing pneumothorax as a therapeutic measure. Adams, in 1887, published the notes of a case of pulmonary tuberculosis in which profuse hemoptysis was associated with a large pulmonary cavity. With the sudden onset of pneumothorax the bleeding at once stopped and improvement in the patient's condition began. He also suggested the advisability of inducing pneumothorax under certain circumstances, but neither Carson nor Adams put the suggestion into practice. In 1882 Forlanini reported a number of striking instances of improvement following the occurrence of a spontaneous pneumothorax, and advised inducing pneumothorax in appropriate cases of pulmonary tuberculosis. In 1892 he began to practice the method, and in 1894 presented his observations before the Eleventh International Medical Congress held at Rome. In 1895 he reported the cure of a

\* Those further interested in this subject can secure a reprint with twenty complete case histories from Dr. Louis Hamman, 714 Park Avenue, Baltimore.



case of grave pulmonary tuberculosis following the prolonged maintenance of pulmonary collapse with nitrogen gas. Although Forlanini continued to use the treatment he published no further reports upon the subject until 1906, since when a number of valuable contributions have come from his clinic.

In 1898 Murphy, though uninformed of Forlanini's work, was led on by the same considerations to use the method. He presents the records of five patients with pulmonary tuberculosis treated by nitrogen inflation of the pleural cavity. All showed striking immediate benefit from the treatment but none, at the time the report was made, had been under observation long enough to allow any conclusions to be drawn about its ultimate value. During the same year Schell published a brief note of a single case in which severe hemoptysis was controlled by inducing pneumothorax. In 1899, Lemke, a pupil of Murphy, presented a preliminary report of 53 cases treated by the method, but owing to the unfortunate death of the author, a fuller account never appeared. Apparently therapeutic pneumothorax was then abandoned in this country, for there are no further reports of its use until the past year, when Lapham, Rothschild, and Robinson and Floyd again have called attention to the procedure.

In 1906 appeared the first article by Brauer upon induced pneumothorax, and since this date the literature on the subject has been enriched by notable contributions from Brauer and his students. He has done more than any other observer to work out the fundamental mechanical and physiological principles of pneumothorax, and has brought valuable clinical and pathological material to the study of the method.

#### SELECTION OF CASES FOR TREATMENT.

The application of induced pneumothorax has not been restricted to any particular disease or type of case. It has been made use of chiefly in pulmonary tuberculosis, but Brauer, Schmidt, Wellman, and others have similarly treated patients with bronchiectasis and chronic non-tuberculous infections of the lungs. It is evident that one-sided lesions are the most favorable, but in the late stages of pulmonary tuberculosis it is difficult to find strictly unilateral cases. To what extent the opposite lung may be involved, and the patient still be a suitable candidate for the treatment, is variously approximated by different observers. Forlanini is lenient in this regard, while Brauer selects his patients with more rigor. It is only reasonable to assume that if immobilization is beneficial, exaggerated activity is harmful. If rest is of value to the diseased lung, we must see to it that the other is not overburdened by the increased demands made upon it. However, it must be pointed out that though both lungs may be affected, the disease is seldom equally active upon the two sides and as the side with the most marked activity is the one usually chosen for the operation, the opposite lung is generally equal to withstanding the added work put upon it. Experience upholds this conclusion, and indeed many observers claim that the untreated side is favorably influenced through the diminished toxemia, and the improved general

condition of the patient that often follow the treatment. Murphy, in his original article, proposed the method particularly for "apical or monolobar tuberculosis in the early stage as the pathological conditions are such that the compression of the lung can be accomplished and adhesions are not likely to be found. I do not consider," he adds, "that it is indicated or practical in advanced or chronic tuberculosis as the fibrous tissue deposited in the lung will not permit compression of the lung nor will the pleuritic adhesions allow of gas injection." In practice Murphy's suggestions have never been carried out. All available reports deal only with cases of advanced pulmonary tuberculosis subjected to the treatment. The method is still on trial, and the tendency has been to establish its value in instances of the disease that have been uninfluenced by the usual hygienic-dietetic measures. When even under unfavorable conditions such value becomes apparent, induced pneumothorax will be given a wider field of application, and we are convinced that the ultimate sphere of its usefulness will be principally in moderately advanced cases of the disease. At present it is impossible to represent statistically the results of the treatment. It is only by studying the results in numerous individual cases that one can form an estimate of its value. Our own experience has been gathered from unfavorable and desperate cases of pulmonary tuberculosis. Many of the patients we operated upon at first were not selected in any medical sense. They were accepted because, conscious of their progressing disease, they were willing to risk a new method of treatment, while more suitable patients withheld their consent. Recently we have induced pneumothorax under more favorable conditions, and hope in the future to find the opportunity to test its value in earlier stages of the disease.

#### THE METHOD OF INDUCING PNEUMOTHORAX.

There are two methods in use for inducing pneumothorax, the method advocated by Brauer, and the method originally used and still employed by Forlanini.

1. *Brauer's Method.*—He calls his method the Brauer-Murphy method, although the procedure recommended by Murphy is certainly much more like the operation of Forlanini. Murphy describes his operation thus: "A tenotomy puncture should be made through the derma; this allows the trocar to be easily inserted. The stilette in the trocar should be withdrawn when the rib is reached; the gas should now be turned on; the trocar should then be pushed inward, hugging the margin of the rib. When the parietal pleura is punctured the trocar advances rapidly and the gas begins to flow freely into the cavity unless adhesions exist. If adhesions be present the gas will not flow. The trocar should be taken out and inserted in the same manner in another position." Although Brauer's method is more complicated than Forlanini's, he warmly advocates it, claiming it is free from certain dangers which he believes the simpler method cannot safely avoid. About half an hour before the operation the patient receives a quarter grain of morphine. The location of the incision having been selected, the patient is arranged upon the table with this

area as the highest point. Unless there is some contraindication, the fifth or sixth intercostal space in the axillary area is chosen. Cushions are placed beneath the patient so that this portion of the chest will protrude and the ribs be held apart. Under cocaine anesthesia the skin, fascia and superficial muscles are divided by an incision five to seven centimeters in length. Through the incision the fascia of the intercostal muscles is divided and the fibres of the muscles separated with dull scissors or a small clamp. Through this opening the parietal pleura can be inspected, and its appearance indicates the presence or absence of adhesions. A dull cannula with an eye situated upon the side near its point is then thrust through the parietal pleura into the pleural space. The cannula is large enough to admit a small ureteral catheter and in certain cases Brauer uses a catheter to palpate the pleural cavity to determine the extent and density of pleural adhesions. If by appropriate observations it is evident that the cannula is in the pleural cavity and the pleural cavity is relatively free from adhesions, gas previously warmed to the body temperature is slowly allowed to run in. Brauer insists that at the first operation from 500 to 1000 cc. of gas should be introduced, since smaller amounts make the subsequent refillings less certain and more dangerous.

2. *Forlanini's Method.*—He, without anesthesia, introduces a small caliber aspirating needle connected with a suitable apparatus through the intercostal space, and thrusting it carefully forward ascertains when the point is in the pleural cavity by manometric readings. If the observation indicates that the needle is in the proper position the gas is then allowed to flow in. At the first operation Forlanini introduces only from 200 to 300 cc. of nitrogen, and gradually produces collapse by the further daily addition of small amounts until a complete pneumothorax has been produced.

After the first inflation the pneumothorax is enlarged and maintained by repeated injections of nitrogen. If the primary operation has been successful, physical examination, and particularly X-ray examination, indicate the position and extent of the pneumothorax and the secondary inflation can be carried out with safety and ease. For secondary inflations ordinary aspirating needles are employed in both methods.

As the object of the treatment is to maintain constant and, as nearly as possible, uniform collapse of the affected lung that gas is most desirable for injection which is least quickly absorbed. It has been found that nitrogen resists absorption from the pleural cavity longer than any other innocuous gas, and for this reason it is generally employed. Air may be used with equal success, but subsequent refillings must then be made more frequently.

Forlanini's method has decided advantages over the procedure advocated by Brauer. It is simpler, causes the patient very little pain, and therefore if local adhesions prevent the successful inflation of the pleural cavity at the first attempt, one may with good grace repeat the effort a number of times until finally perhaps a point is found where the pleural space is patent. Such an experience is by no means uncommon. It would be a formidable procedure to repeat the Brauer

method five or six times. Brauer does not claim simplicity or ease for his method. He recognizes all the advantages that the Forlanini method has in this direction, but he urges that the latter operation is attended by grave danger, and therefore justly prefers to put himself and the patient to some inconvenience to avoid taking what he considers an unjustifiable risk.

The dangers attending induced pneumothorax are two, infection and air embolism. Infection of the pleural cavity may occur from without or through the lung. It is needless to emphasize the ease with which the pleural cavity may be infected, and superfluous to insist upon the importance of a rigid and irreproachable surgical technic in all the manipulations. With the necessary precaution, infection of the pleural cavity from without will rarely occur. However, v. Muralt, who is an able and efficient man, reports an instance. A patient operated upon by the Brauer method developed a stitch abscess and following this a rapidly fatal pyopneumothorax. One of our patients developed pyopneumothorax, possibly as the result of faulty technic. Infection of the pleural cavity through the lung may occur if the lung is injured by the needle during manipulation to find the pleural cavity, or by spontaneous rupture, or through a tear of the organ occasioned by the pull of adhesions when the pneumothorax is subjected to high pressure. Of these three possibilities we may say that we know of no instance in which the lung has been torn by adhesions, although Keller reports a case in which it is presumed to have happened. Knoblauch reports the development of local empyema in a patient operated upon by the Forlanini method. v. Muralt cites a case in which spontaneous rupture of the lung occurred during a secondary refilling. In advanced pulmonary tuberculosis such ruptures happen not infrequently, and perhaps this instance was not occasioned directly by the treatment.

More important than the danger of infection is that of air embolism. A few instances will illustrate its gravity. Lemke, in inducing pneumothorax, did not use a manometer, but determined that the needle was in the pleural cavity by instructing the patient to take deep breaths. An inrush of air occurring during inspiration indicated to him that the needle was in the proper position. At the second inflation upon a patient with extensive right-sided disease, the usual sound of inrushing air was missed. After two or three forced inspirations about three cubic inches (48 cc.) of nitrogen had been sucked in when the patient complained of feeling weak, became pale and fell into a state of collapse. Respirations were stertorous, the pulse slow and weak. The needle was withdrawn and stimulants administered. As soon as the pulse improved, a careful examination was made and revealed complete right-sided hemiplegia. When the patient became conscious he had aphasia. Within twenty-four hours paralysis of the face had disappeared. Some months later the face was normal, the leg weak and spastic, and the arm had regained but little power. During a refilling, while nitrogen was flowing in through the needle, one of Brauer's patients suddenly moved. She complained at once of great pain, became uncon-

scious, and collapsed. After several hours there was evident hemiplegia, and six hours after the operation the patient died. A patient in whom pneumothorax had been successfully induced was allowed to wait too long for refilling, and the gas had been almost completely absorbed. At the second operation, although no characteristic manometric variations occurred, it was supposed that the opening of the needle was in the pleural cavity. Thinking the needle might be plugged, a little nitrogen was allowed to run in. The patient immediately collapsed, and in a few minutes was dead.

It is needless for Brauer to say that to have personally lived through such an experience leaves an ineffaceable memory of its horror, and a grim determination to save no effort to avoid its repetition. It is on account of the danger of air embolism that he so insistently urges the use of his method, in spite of the difficulty for the operator and inconvenience for the patient.

These unfortunate clinical results have not been reproduced experimentally. The lungs of healthy animals withstand, as Brauer himself asserts, a remarkable amount of trauma. He was unable to produce fatal air embolism in dogs, in spite of gross damage to the lung. However, operating with an aspirating needle, he found it impossible to reach the intrapleural space without producing some slight lesion of the visceral pleura. He believes that when the lung is diseased, even such trivial lesions may have serious consequences. Forlanini repeated these experiments. With great ease he could induce pneumothorax in dogs and upon forcibly inflating the lungs after removal from the body, rupture always occurred first about the borders, and never at the position corresponding with the point of operation.

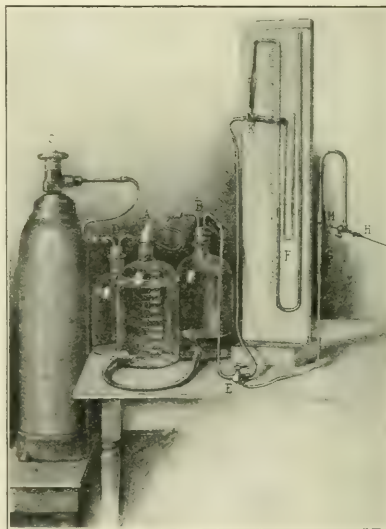
It is well known that large amounts of air may be injected into the systemic circulation without producing fatal air embolism. If large amounts are rapidly injected into the veins, death occurs from dilatation of the right ventricle and cardiac syncope. Ten to twelve cubic centimeters of air per minute may be allowed to flow into a vein for an hour without producing any serious results. Fatal air embolism of the brain never follows the introduction of air into the systemic veins. Air introduced directly into the left ventricle or into the carotid artery produces immediately symptoms of cerebral embolism. Only very small amounts can be injected without danger. Forlanini finds that from six to eight cubic centimeters in the ventricle and from two to three cubic centimeters in the carotids may be safely given.

Simple puncture of the lung with an aspirating needle, even when the organ is diseased, is associated with little danger. Daily exploratory punctures are made without hesitation in all large medical clinics. Serious air embolism has followed attempts to produce pneumothorax only upon the injection of gas in the absence of satisfactory evidence that the needle is in the pleural cavity. We believe that when proper care is exercised the puncture method is quite safe, and in our hands it has given the utmost satisfaction. It is pertinent to note that of the four fatal cases reported by Brauer, the fatal case and instance of hemiplegia by For-

lanini, and the instance of hemiplegia by Lemke, five of the seven serious complications occurred during secondary inflations. As the same method of refilling is used by all observers, Brauer's operative procedure does not remove the risk accompanying the subsequent injections.

#### THE METHOD OF INDUCING PNEUMOTHORAX USED BY THE AUTHORS.

The apparatus we have used is a modification of Brauer's. It is extremely simple, and the accompanying illustration shows its construction. Our earliest cases were inflated with air, later we employed nitrogen gas supplied, compressed in cylinders, by the Linde Air Products Co. *A* and *B* are bottles of two litre capacity, with outlets at the base connected with



rubber tubing. One of the bottles is graduated. Bottle *B* is fitted with a two-hole rubber stopper, into which two pieces of bent glass tubing are inserted. One of the tubes is connected with the nitrogen tank *C*; a wash bottle *D*, containing a 1 to 500 bichloride of mercury solution, is inserted between the bottle and the tank. The second tube is connected with a three-way stop-cock *E*, which in turn is connected through one arm with the manometer *F*, and through the other with the needle *H*. A sterile filter, *G* (a glass tube lightly packed with absorbent cotton), is inserted between the stop-cock and the needle. The manometer consists of two tubes, the outer for water, the inner for mercury. By means of the cock, *K*, the one desired may be connected with the instrument. The mercury manometer was added to be used under high pressure, but as we, in our work, have avoided high pressure, it is superfluous. The needle is fitted upon an attachment with a two-way stop-cock *M*. When the cock is turned transversely, the bore of the



needle is connected only with the lumen of the rubber tubing. When, as frequently happens, it is desired to clear the lumen of the needle, the cock may be turned and a wire introduced into the needle. The wire is bent so that its end will just reach, and not protrude beyond, the tip of the needle. Any desired degree of positive or negative pressure may be created in the system by elevating or lowering bottle *A*. When the handle of the stop-cock *E* is turned towards *a*, the bottle *B* is directly connected with the lumen of the needle *H*, and if bottle *A* be elevated, gas will flow through the needle. If the handle be turned to *b*, the lumen of the needle, *H*, is connected with the manometer *F*, and the pressure at the point of the needle recorded. If the handle be turned to *c*, the bottle *B* is connected with the manometer *F*, and the pressure in *B* registered.

Before beginning the operation, all of the tubing and stoppers are sterilized. Dry sterilization is best, for a few drops of water in the system will prevent the satisfactory registration of pressures. Of course the filter *G* is dry sterilized. The apparatus is then connected up, except that the tubing running from *b* to the needle is not added. The bottle *A* is then filled with warm bichloride solution (1 to 500) and elevated and the lever of the stop-cock *E* turned towards *a* so that the solution will flow from *A* into *B*. When *B* is completely filled, the lever is turned towards *b*. The system in the bottles is thus closed and *A* may be lowered without the solution in *B* running back. The cock upon the tank *C* is then carefully opened and as much gas (*N*) as may be desired is allowed to run in and displace the bichloride solution in *B*.

If a number of patients are to receive injections, whenever the gas in *B* has been used more may be added as desired, without disturbing any of the connections. When the operator is prepared to begin, he takes the two pieces of rubber tubing connecting the needle with the stop-cock from the sterile package and inserts the filter between them. An assistant slips one end of the tubing over the arm of the stop-cock, the operator connects the other with the needle. The wire is withdrawn from the needle and the cock turned transversely. To insure that the tubing is patent and the filter not too tightly packed, the lever of the three-way stop-cock *E* is turned to *c*. The manometer shows the pressure in *B*. If the lever be now turned to *b*, the pressure will fall at once to zero, if the tubing from *H* to *F* is free; if the needle or tubing is occluded, the pressure will not fall; if partially occluded the pressure falls slowly. The lever is then turned to *a* to insure that the gas from *B* flows freely through the needle, and is finally turned to *b*, and the operation begun with normal pressure in the needle connected with the manometer.

For the first inflation a blunt needle with rounded edge is used, a needle even less pointed than those usually employed for lumbar puncture. The bore of the needle should measure from 1 to 1.5 mm. in diameter, as smaller needles easily become plugged either with blood or bits of tissue, and transmit less satisfactorily the variation in pleural pressure. The point for operation having been selected, the skin is infiltrated with a weak solution of cocaine, and with a small scalpel the

skin and subcutaneous tissues are punctured. The needle is introduced and carefully pushed obliquely forward into the interspace. Usually marked resistance is offered by the fascia of the intercostal muscles and the needle finally pierces it with a sudden pop, which is well felt and often heard. One is then sure that the point of the needle lies amongst the fibres of the intercostal muscle and another cautious advance forces it directly into the pleural space. The operator has the manometer before him, and if the pleura be not adherent, as soon as the point of the needle reaches the pleural space, the manometer records a marked negative pressure with wide respiratory variations. The extent of the variation depends upon the force of the respiratory efforts, usually equaling about minus 8 to minus 10 cm. water on inspiration, and minus 3 to minus 6 cm. on expiration.

When the pleural cavity is free from adhesions the operation invariably goes smoothly. When adhesions are present it is more complicated: (1) since the characteristic pleural variations in pressure are absent, and therefore one cannot tell with certainty when the needle is in the pleural space, and (2) collapse is rendered difficult and if the adhesions be dense, impossible. Various measures have been suggested to overcome these obstacles. Forlanini introduces the needle to a point where he thinks the pleural surface has been reached. He then very slowly and cautiously pushes the needle a little further in, and at each advance tests the position of the needle. For this purpose he compresses a small area of the rubber tubing between the fingers, thus forcing through the needle a very small amount of gas under high pressure. If the needle is in the extrapleural tissue the manometer will show a negative pressure equal to the amount of nitrogen expelled from the tubing. Should the gas vesicle be in close proximity to the pleura, respiratory variations may be recorded but they are usually small in extent. If the point of the needle is between the two layers of the pleura and the expelled gas separates them, a more marked negative pressure is recorded than could be accounted for by the amount of nitrogen injected and the respiratory variations are wider. If the needle is in the lung, the manometer oscillates with respiration but the mean pressure is about zero. If the needle is in the extrapleural tissue, or in a mass of dense pleural adhesions, the pressure rapidly rises, as gas is introduced in larger amounts, and gradually falls to normal as the gas diffuses throughout the tissue. Thus, in the instance of pleural adhesions emphysema of the connective tissue is produced instead of pneumothorax.

In the presence of adhesions Saugman introduces the needle into the lung. The oscillations of the manometer indicate its position. The needle is then cautiously withdrawn until the oscillations cease. With a syringe that fits into the end of the needle, aspiration is performed. If no blood is obtained, he forces in nitrogen under a pressure of from 20 to 30 cm. water. If the pleura separate, a well-marked negative pressure may occur after a few cubic centimeters of nitrogen have been injected. Larger amounts of gas may then be allowed to run in, although the operation is usually attended with great pain from the stretching and tearing of adhesions.

As we have stated, when the pleura is free, the operation of

inducing pneumothorax is extremely simple. We have, in a few instances, when we were confident that the needle was in the pleural cavity, attempted to break up adhesions by injecting air under pressure. After from 50 to 100 cc. of gas have been injected, the patient complains of extreme pain and the manometer registers a high, positive pressure, often 15 to 20 cm. water. During the following few minutes the pressure gradually falls to again rise as more gas is introduced. In this manner many hundred cubic centimeters may be injected, although the pleural surfaces remain adherent, and no pneumothorax is produced. We have, however, abandoned such ill-advised attempts. There is always danger of air embolism, and the infrequent success of efforts to forcibly separate an adherent pleura does not justify assuming the risk assumed. When we are unable to clearly find a pleural space, instead of manipulating the needle, we prefer to withdraw it and try in another position. The procedure gives so little discomfort to the patient that one does not hesitate to make numerous punctures in a search for a clear pleural space. In this way all danger of air embolism is avoided. In one of our cases we made three fruitless efforts in the axillary region to hit the pleural cavity, but the fourth, made in the back below the angle of the scapula, was successful. A partial pneumothorax was produced, which after subsequent refillings, extended and has become complete. In another instance eight attempts were made to induce pneumothorax, but to no avail. Another patient, in whom no pleural cavity could be demonstrated, was later operated upon by the Brauer method. The blunt canula entered a dense network of pleural adhesions and it was impossible to bring about a pneumothorax.

When adhesions are present and a small intrapleural air vesicle has been produced, Saugman advocated using high pressure to break up the adhesions. He for months maintained a pressure of from 20 to 30 cm. water in the cavity. If the adhesions are dense, it is impossible to separate the pleura and the method frequently produces unpleasant results. Subcutaneous emphysema spreading over the thorax and abdomen is not uncommon. Less often, but more serious in its consequences, air enters the loose connective tissue between the costal pleural and the thoracic fascia and reaches the mediastinum. It may appear in the subcutaneous tissue of the neck and cause great pain, and by pressure on the esophagus, difficulty in swallowing. Instances are reported in which the gas has pierced the diaphragm, probably in the connective tissue surrounding the aorta, and produced extensive subdiaphragmatic emphysema.

It is true that pleural adhesions frequently stretch, and under continued gentle pressure, allow the lung to completely collapse. If a fairly large air vesicle has been produced and the mediastinum is rigid, one may, with little discomfort to the patient, maintain an expiratory pressure of from 5 to 15 cm. of water, and note the gradual extension of the pneumothorax cavity and increasing collapse of the lung. There is always some, and often severe, pain where adhesions are attached.

If the adhesions are dense and, upon repeated punctures in

different locations, no free pleural space can be found, it is wisest to abandon the attempt. Efforts to forcibly tear the adhesions under high pressure seldom succeed, and are attended by danger of air embolism and deep emphysema.

Pleural adhesions are then the main obstacle in the way of successfully inducing pneumothorax, and unfortunately their presence or absence cannot always be determined before the operation is undertaken. When the history of the illness points to frequent attacks of pleurisy, and particularly when physical signs indicate a thickened pleura, we are prepared for failure. When fluoroscopic examination and percussion on inspiration and expiration show a wide excursion of the lower lung border, we are equally confident that the operation will succeed. It is when the diaphragm movements are limited and there is no pleural dullness that definite predictions cannot be made. The diseased lung, as well as pleural adhesions, restricts movement, and while a lack of proportion between the extent of disease and the amount of restriction may be a valuable indication, we cannot be certain of the result. If compression of the lung has been begun by a pleural exudate, one may maintain and increase the collapse by withdrawing the fluid and introducing gas. As the pleural surfaces are already separated there is no difficulty in finding the space. When the gas is introduced through the effusion, we are deprived of the information afforded by the manometer, as the pressure variations are not transmitted through the fluid.

The amount of gas to introduce at the first inflation depends, in a measure, upon the condition of the patient. If severe pain or dyspnea develop, only a few hundred cubic centimeters should be injected, otherwise it is advisable to give from 500 to 800 cc. Forlanini and Saugman advocate giving from 100 to 200 cc. and very gradually, by daily repetitions, to increase the amount. They feel that, in this way, the contents of the chest adjust themselves more satisfactorily to the changing conditions of pressure. However, we believe the importance of at once producing an appreciable collapse of the lung, so that subsequent inflations may be carried on without danger of piercing the organ, far outweighs this consideration. As a matter of experience, from 500 to 800 cc. of gas may be introduced into the pleural cavity, even when the opposite lung is extensively diseased, without occasioning any unpleasant symptoms.

If the original inflation has been successful, the subsequent operations may be performed with great ease. A careful physical examination will usually indicate the position and extent of the pneumothorax, although X-ray examinations add wonderful precision to the observations. Stereoscopic plates, particularly, give an exact picture of the conditions and show the position of the lung and depth of the cavity at every point. For the second and subsequent injections a sharper needle of smaller bore may be used. If the lumen of the needle is free as soon as it enters the pleural space, the characteristic manometer oscillations occur and the gas should never be allowed to flow in if they are absent. When fine caliber needles are employed they frequently become plugged by a drop of blood or serum, or a bit of the subcutaneous fat. They may readily be cleaned by

introducing the obturator in the manner previously described. If the needle is in the pleural cavity, the manometer will then at once show respiratory variations and the gas is allowed to run in slowly under slight positive pressure. After each 100 cc. the pleural pressures are read, and the amount introduced largely regulated by the pressure conditions.

In the beginning inflations are made every second or third day. When the collapse is complete once a week suffices. Later, as the pleura loses its capacity for absorption, inflations at two and three-week intervals will maintain the collapse. At each inflation one estimates the amount of gas that has been absorbed by the amount necessary to bring the pleural pressure to the level of the end pressure of the previous inflation. Before collapse is complete, a few hundred cubic centimeters additional gas are added at each operation. Subsequently, if the pleural cavity is free, the pressure should be maintained that gives a slight positive elevation on inspiration. The normal pleural cavity absorbs from 80 to 100 cc. nitrogen per day; after the pneumothorax has existed for some months it absorbs from 25 to 50 cc. The pressure conditions vary somewhat in each individual case, and the amount of gas injected and the frequency of the inflations must depend absolutely upon the manometric record. When the pleural cavity is free it requires from four to five inflations before a positive pressure is reached. If adhesions are present, partly occluding the pleural cavity, a positive pressure may be recorded after the first inflation of from 500 to 800 cc. Under these conditions a moderate positive pressure is maintained, and not infrequently the adhesions will subsequently yield. The pressure records in Case 13, with a free pleural cavity, and in Case 15, with a partially adherent pleura, illustrate the points.

The pneumothorax may be maintained for a year or more and the lung be then allowed slowly to expand.

Throughout the whole procedure of inducing and maintaining pneumothorax, the manometer plays such an important part in guiding us that we shall briefly review the information it gives.

1. It indicates accurately when the needle has entered a free pleural space. The manometer at once records a negative pressure with marked respiratory variations.

2. When the needle is in the lung respiratory oscillations occur, but they vary about the zero point. If the patient draws a deep breath and holds it the manometer records a sudden negative pressure which quickly falls to normal. If the needle is in the pleural cavity, the negative pressure is maintained as long as the breath is held.

3. It indicates the size of the pleural space. If the pleura is free many hundred cubic centimeters of gas must be introduced before the pressure is raised. If the pleura is partially obliterated or the pneumothorax cavity walled off, 500 or 600 cc. of gas may bring the pressure to zero. If the cavity be small, a few hundred cubic centimeters may occasion a marked positive pressure. In walled-off spaces the respiratory variations are smaller than in the free pleural cavity.

4. If the needle be extrapleural or be imbedded in pleural

adhesions, no respiratory variations occur. If a small amount of gas be injected the manometer records a high positive pressure, which gradually falls to zero as the gas diffuses.

5. It indicates the absorbing power of the pleura, and accurately controls the frequency and amount of injections necessary to maintain the desired conditions.

6. It indicates the degree of elasticity of the compressed lung. Upon subsequent refillings, if there is a very gradual rise in pressure following the introduction of each 100 cc. of gas, the lung has expanded with the diminishing pleural pressure. If the lung has remained collapsed, there is little rise in pressure following the introduction of the first few portions of gas, and then a very sudden and marked rise upon the introduction of a further small portion.

7. Likewise a slow increase in pressure with wide respiratory variations indicates a flexible mediastinum; a rapid increase in pressure with small respiratory variations, a rigid mediastinum.

8. v. Muralt has observed a sudden fall in pressure during inflation, due to the giving way of pleural adhesions. In another instance the lung ruptured during an inflation and the pressure fell at once to zero, and showed no subsequent rise even when large amounts of gas were introduced.

9. Occasionally, the manometer shows reverse respiratory oscillations; that is, a higher pressure with inspiration than expiration, due to paradoxical movements of the diaphragm.

#### THE PATHOLOGICAL ANATOMY OF THE COLLAPSED LUNG.

Forlanini, Saugman, Graetz, Warnecke, and Kistler have published descriptions of the lung after months of collapse. When collapse has been complete the lung is a firm mass lying close to the spinal column. Histologically the following conditions are found:

1. The most striking change is the extreme fibrous tissue formation. This has been noted in every instance and occurs in a degree never observed under other conditions. Bronchi and alveoli may be compressed, and the scattered aveoli imbedded in the connective tissue give the organ the appearance of a gland. The overgrowth of connective tissue is more marked in the situations where compression has been complete, than in portions of the lung that have been prevented from collapsing by adhesions. A similar tendency to fibrous tissue formation is not observed in the opposite lung.

2. While evidence of advancing disease may be found in the opposite lung, the collapsed organ shows no fresh lesions. Old caseous areas may be seen surrounded by dense fibrous tissue, but no recent tuberculous infiltration.

3. The epithelium of the alveoli is transformed and becomes cuboidal or columnar in type.

4. The lymphatics are markedly dilated and pigment richly deposited.

Bruns, in an experimental study of the effects of pneumothorax, has shown that the amount of blood in the collapsed lung has decreased a few hours after the pneumothorax has formed and becomes less and less as collapse proceeds. Histologically he finds that in spite of long standing atelectasis,



the alveolar walls, although pressed together, display no tendency to adhere. The epithelium remains intact and the lungs may, at any time, be successfully reinflated. In the region of the large vessels and bronchi there is definite proliferation of connective tissue. The right side of the heart hypertrophies, consequent upon the interference with pulmonary circulation, although the diminished suction action of the lungs and diaphragm may play a part in its production.

Besides the functional rest that pneumothorax induces, there is, then, a decided tendency to fibrous tissue proliferation. The latter process may depend entirely, or in part, upon the altered circulatory conditions in the lung, and the occurrence of marked stasis in the lymphatic system.

#### THE CLINICAL SYMPTOMS OF INDUCED PNEUMOTHORAX.

The effects of inducing pneumothorax upon the clinical symptoms may be divided into those resulting from the pneumothorax itself and the changes it occasions in the pre-existing symptoms. It is remarkable how well borne the procedure is, even by patients with advanced bilateral disease. If the pressure in the pleural cavity be raised only a little above zero and the patient be kept at rest, there is seldom more than a feeling of fulness in the chest and at times a little dyspnea. When complete collapse is obtained, if the opposite lung be unaffected, or but slightly diseased and grave constitutional symptoms are absent, patients even with a pressure of from 10 to 15 cc. of water do not suffer inconvenience, other than a little dyspnea on exertion. At the Eudowood Sanatorium they assist in household duties and in light work about the grounds. One of our patients (Case No. 3) is running a chicken farm near Baltimore and comes to the dispensary every two weeks for reinflation. He is not embarrassed in the performance of his work except when, as he says, he forgets and attempts to run. During the production of the pneumothorax pain is frequently complained of. When there is X-ray control, it is found that the pain is usually situated in the region of adhesions. We have frequently noted that epigastric pain follows early inflations, due, perhaps, to diaphragmatic adhesions. In one instance an attack of pleurisy with effusion gave rise to severe pain. The usual view is that the pain of pleurisy is due to the rubbing together of the inflamed pleural surfaces. This patient had complete pulmonary collapse, and though apposition of the pleural surfaces was impossible, there was intense pain.

Upon the pre-existing symptoms pneumothorax has a striking effect. The cough and sputum may be increased for a few days, but they rapidly diminish after a few weeks, and completely disappear if the lung collapses fully and the opposite organ is unaffected or harbors a quiescent lesion. Nothing in the whole procedure is so striking as this effect upon the frequency of cough and the amount of sputum. Patients with from 50 to 100 cc. of expectoration per day may be almost sputum free three or four weeks after treatment is begun. Even when adhesions permit of only partial collapse of the lung, a diminution of the amount of sputum always occurs.

As the sputum diminishes, the number of tubercle bacilli decreases and frequently bacilli entirely disappear. The temperature may be elevated above the previous level for a few days following the first injection, but thereafter rapidly falls and usually remains about the normal. With the decrease of fever the appetite increases and the general condition is markedly improved. At first there is almost constantly a loss of weight, which later is usually rapidly regained. Upon hemoptysis the procedure has a most beneficial influence. In a number of our cases hemoptysis promptly stopped after the first inflation. We recall the interesting instance of Schell. Rothschild has emphasized particularly this feature of the treatment.

With but a small number of cases it is impossible to express the results of the treatment numerically. The character of the cases varies so widely that statistical studies would permit no respectable inference. For a time, at least, the results obtained in individual instances must be used to fortify the claims made for the method. For this reason we add the records, in sufficient detail, of the twenty patients upon whom we have induced pneumothorax and summarize our results and present our impressions.

#### REVIEW OF CASES.

Since all the cases here reported were suffering from moderately or far advanced pulmonary tuberculosis, it would be futile to gauge the value of pneumothorax treatment by classifying them according to the stage of the disease. As we have insisted, a just estimate of the value of the treatment may be gained only by a study of the individual instance. However, some general grouping is desirable and therefore we divide the cases according to the success attending our efforts to produce collapse of the diseased lung. There are four groups:

- I. In three instances (Cases 5, 10, and 17) induction of pneumothorax was followed by death or a serious complication.
- II. In three instances (Cases 6, 7, and 14) it was impossible to produce pneumothorax.
- III. In seven instances (Cases 2, 4, 8, 11, 15, 16, and 18) only an incomplete pneumothorax was produced.
- IV. In seven instances (Cases 1, 3, 9, 12, 13, 19, and 20) a complete pneumothorax was produced.

*Group I.*—Case 5, with extensive pulmonary tuberculosis and pleural effusion, developed a pyopneumothorax after the first inflation. While it is possible that the infection of the exudate may have come from the lung it seems more likely that it depended upon a faulty operative technic. The symptoms following the injection overshadowed any favorable influence the pneumothorax may have exercised and treatment was promptly abandoned.

Case 10 developed evident symptoms of tuberculous meningitis after the third inflation, followed by death fourteen days later. Tuberculous meningitis is not an uncommon terminal event in pulmonary tuberculosis and we are disinclined to allow that the pneumothorax was responsible for its occurrence.

A definite conclusion cannot be reached, but if the pneumothorax was the direct cause, the mechanism by which the meningitis was produced is not easy to explain.

Case 17 was in a desperate condition when treatment was begun. Only two inflations were given, the patient dying 10 days after beginning the treatment. The pneumothorax lessened the cough. We are convinced that the treatment did not hasten the patient's death.

*Group II.*—In Cases 6 and 14 no pneumothorax could be produced, owing to the pleural adhesions. In Case 6 the Forlanini and the Brauer methods both were fruitlessly employed, and in Case 14 five attempts in different positions were made without success. In Case 7, although we were able at each operation to introduce a few hundred cubic centimeters of gas, the immediate rapid rise of pressure after the introduction of small amounts of gas followed by a gradual fall to normal, and the absence of satisfactory respiratory variations in pressure indicate that no true pleural space was formed, the gas diffusing through the pleural adhesions. The course of the disease in these three cases was entirely uninfluenced by the treatment.

*Group III.*—As stated in the text, Cases 2 and 4 were hopelessly advanced when the treatment was instituted. Under the most favorable conditions they were rapidly going down hill. The treatment was begun at their request, and on our part with the desire to demonstrate the harmlessness of the procedure rather than with the expectation of obtaining any permanent benefit. The cases are interesting as examples of patients with extreme bilateral pulmonary involvement displaying little distress, although there was extensive collapse of one lung with an expiratory pleural pressure of 7 cc. of water and marked dislocation of the mediastinum. The condition is in striking contrast to the clinical picture after spontaneous pneumothorax in advanced pulmonary tuberculosis. In both cases there was reduction of cough and sputum, but the general condition was uninfluenced and the disease continued to progress.

In the other five cases in this group one lung was totally or almost totally involved, and there was a definite but not extensive lesion of the other lung. In four cases the right lung was more extensively involved than the left; in Case 18 the reverse was true. In all five the upper lobe was the seat of the most marked lesion, and it was adhesions over the upper lobe that prevented complete collapse. In Cases 8, 16, and 18 the production of pneumothorax was followed by diminution of the cough and amount of sputum. In Case 11 there was gradual lessening of cough and sputum, marked reduction not occurring until after the advent of the pleural effusion. The effect upon hemoptysis in Case 16 is noteworthy. In Case 15 the sputum was a little decreased but the cough was aggravated.

Three of the patients showed marked improvement in their general condition and in the constitutional symptoms (Cases 8, 11, and 16). In Case 15 treatment was abandoned and Case 18 was under observation only a short time. We wish to call particular attention to the improvement in Case 8.

*Group IV.*—In all seven cases there was well marked disease of one lung, with some involvement of the opposite. In the three Cases 3, 13 and 20 the right lung was the more severely diseased; in four Cases 1, 9, 12, and 19 the left. In all seven cases pneumothorax was followed by a diminution of cough and expectoration. Six of the seven cases (all save No. 1) had hemoptysis of varying grade, which did not recur after the pneumothorax was complete. All of the patients showed marked improvement in their general condition except Case 9, who lost considerable weight but was otherwise well. In Case 12 the disease progressed somewhat in the opposite lung. Cases 19 and 20 were under observation but a short time. Cases 1, 12 and 13 developed pleurisy with effusion. We wish to call special attention to the excellent recoveries made by Cases 1, 3, and 13.

#### CONCLUSIONS.

1. Induced pneumothorax is a harmless procedure and the operation, carefully performed, is without danger.
2. In 3 out of 20 cases it was impossible to produce any pulmonary collapse owing to general pleural adhesions.
3. Of 16 cases in which pneumothorax was successfully produced, in but 7 was the pneumothorax complete.
4. Of 9 cases with induced pneumothorax existing for four months or longer 4 have developed pleurisy with effusion.
5. The pneumothorax has, in most instances, an immediate and striking influence upon the cough and expectoration. Tubercle bacilli may disappear from the sputum.
6. Constitutional symptoms abate more slowly. In most instances there is at first a loss in weight followed by a gradual rise.
7. The total collapse of one lung causes surprisingly little inconvenience. Usually there is but slight dyspnea on exertion. Many of the patients with an induced pneumothorax assist actively in the work about the sanatorium.
8. The procedure is of great value in the treatment of pulmonary hemorrhage.
9. While induced pneumothorax will never become a routine method for the treatment of pulmonary tuberculosis, still in selected cases it offers a prospect of temporary and permanent relief when the usual methods of treatment have been unsuccessfully tried. Quiescent lesions in one lung with acute recrudescence in the other are the most favorable for the treatment. Its use need by no means be limited to strictly unilateral lesions, but when there is advanced disease of both lungs little benefit can be expected. It would seem advisable not to withhold the treatment until the patient is hopelessly advanced, but to apply it judiciously to suitable moderately advanced patients in whom the disease tends to progress in spite of appropriate treatment.

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## NOTES ON NEW BOOKS.

*The Sexual Life of the Child.* By DR. ALBERT MOLL. Translated from the German by DR. EDEN PAUL. \$1.75. (New York: The Macmillan Company, 1912.)

This is an attempt at the study of individual psychosexual development, normal and abnormal from infancy to maturity. The material is from the author's large personal observation of cases and these case histories, with numerous well-chosen citations from the literature and comments thereon make the bulk of the book.

However, satisfactory explanation of the phenomena described is entirely lacking. The work of Freud, Jung, Stekel and others, which has thrown so much light on the psychology of the unconscious, is practically unknown to the author, though some of Freud's earlier work is mentioned only to be firmly disagreed with, probably largely because of obvious misunderstanding of it. The statement (p. 14) that "in any case, Freud has not systematically studied the individual manifestations of the sexual life of the child," is amusing. The authors "analysis of the phobia of a 5-year-old boy" covers 105 pages in the 1909 Bleuler-Freud Jahrbuch. The result then is a book of valuable source data, only, and one misses (1) an adequate hypothesis, psychologic or biologic, concerning the nature of the sex impulse, and (2) a conception of the mental mechanisms underlying the manifestations of the sex impulse, which would reconcile the contradictions and show the organic unity of them.

It will serve, however, to draw attention to the neglect of sex instruction, and the serious results of that neglect in children and youth, and emphasize the need, now being more widely recognized daily, of very radical change in hygienic and pedagogic customs in that respect.

*Diseases of the Mouth for Physicians, Dentists, Medical and Dental Students.* By PROF. DR. F. ZINSSER, Cologne. Translated and Edited by JOHN BETHUNE STEIN, M. D., New York. Illustrated. \$7.00. (New York: Rebman Company, 1912.)

The title of this work is misleading, for it deals only with syphilis and similar diseases of the mouth. It is, as such, an excellent contribution to the study of these diseases. The author makes no attempt to treat the whole subject of syphilis, but only as it shows itself in the mouth. The colored illustrations, made from moulages in the collection of Dr. Zinsser are splendid, and each plate, fifty-two in number, is faced by a brief description of the lesion shown. The introductory chapter is brief but furnishes a clear account of syphilis as it is met with in the mouth, and

the translation runs smoothly. It is, however, the illustrations which make this work especially serviceable. There are few institutions in this country that have collections of moulages, from which the best reproductions are secured, and, therefore, the publishers are to be thanked for having published this work in English with such admirably reproduced illustrations.

*Nervöse Angstzustände und Ihre Behandlung.* Von DR. WILHELM STEKEL (Wien). Zweite, Vermehrte und Verbesserte Auflage. \$4.25. (Berlin und Wien: Urban u. Schwarzenberg; New York: Rebman Company, 1912.)

The users of psychoanalysis, as developed by Freud, his pupils and followers, will find this a useful book to add to their library on this subject. Dr. Stekel divides these conditions of anxiety into two classes, a neurosis (*Angstneurose*) and hysteria (*Angst-hysterie*). Under the neuroses he classifies respiratory and cardiac distress, disturbances of digestion, including nausea and vomiting of pregnancy, congestion, loss of consciousness, fainting, trembling, shivering, paræsthesias, cramps, tics, pains and sleeplessness. Under hysteria he classes those cases with obsession, topophobia, blushing, anxiety about travelling in railroads, and examinations, psychical impotency, dizziness and anxiety of high places, stuttering, hypochondria, etc. Where the conditions are often so similar, and where the division is purely arbitrary, careful study alone of individual cases will teach the student whether an individual is suffering from a neurosis or hysteria. The use of psychoanalysis in the elucidation of these troubles requires much time and patience and should only be undertaken by those who are fully acquainted with the responsibility of its employment. Stekel's work will serve not only as a guide to its proper use, but incidentally to a further study of the troubling symptoms he treats by this modern method, which like all new modes of therapy has yet to find its correct place among our means of cure.

*Diagnose und Therapie der Magen und Darmkrankheiten.* Von PRIVATDOZENTEN, DR. WALTER ZWEIF. Zweite, vermehrte Auflage. Illustriert. \$4.00. (Berlin und Wien: Urban & Schwarzenberg; New York: Rebman Company, 1912.)

Written by a pupil of Boas for the general practitioner this book met with approval in its first edition, and should meet with like approbation in its revised form. The author has added a few chapters which somewhat enlarge its scope but do not alter its excellence as a guide to the study and knowledge of diseases of



the gastro-intestinal tract. The first part is general in character, dealing with the physiology of digestion, cures, physical treatment, and that by drugs, etc., while the latter two-thirds of the work is devoted to the diseases of the stomach and intestines, as follows: Acute and chronic gastritis, ulcer, dilatation, cancer, entropsis, nervous dyspepsia, acute and chronic enteritis, chronic ulcerative colitis, sigmoiditis, chronic obstipation, ulcers, cancer, appendicitis, diseases of the large intestine, ileus, and nervous diseases of the intestine. The final chapter describes concisely the chemical and microscopical examination of the gastric contents and faeces. Those who can read German will find Dr. Zweig's work conservative and helpful.

*Life and Letters of Dr. William Beaumont, including hitherto Unpublished Data Concerning the Case of Alexis St. Martin.* By JESSE S. MYER, A.B., M.D., Associate in Medicine in Washington University, St. Louis. With an Introduction by SIR WILLIAM OSLER, Bt., M.D., F.R.S. Regius Professor of Medicine in Oxford University, England. With 58 illustrations. (St. Louis: C. V. Mosby Company, 1912.)

The author explains that the appearance of this book at the present time is to commemorate the hundredth anniversary of William Beaumont's entrance upon the practice of medicine. Upon June 12, 1812, he was licensed in Vermont to practice "physic and surgery."

The book before us is an effort on the part of the author to portray Beaumont not only as a man of science but as a man of forceful personality with peculiar traits of character. The labor of ascertaining the facts of the life of one who lived for many years upon the frontier as an army surgeon has been very great and the author is to be congratulated upon his thorough and conscientious work. The result has been a complete and final biography of a no ordinary man. He had a talent for research and accomplished remarkable results when his period and the difficulties which he encountered in his self-imposed tasks are considered. Had the same opportunity been afforded today to modern investigators for the first time how many would have made more important discoveries than he did respecting gastric secretion? The physiology of digestion, according to Dr. Osler, owes to him the following: "The confirmation of the discovery by Prout of the presence of hydrochloric acid in the gastric juice; the recognition that the essential elements of the gastric juice and the mucous secretion were separate; the establishment by direct observation of the profound influence of mental disturbances on the secretion of the gastric juice and on digestion; the fuller and more accurate comparative study of digestion in the stomach with digestion outside the body; the rapid disappearance of water from the stomach through the pylorus; the first comprehensive and full study of the movements of the stomach; the study of the digestibility of different articles of diet, which remains to-day one of the most important contributions ever made to practical dietetics; the relation between the amount of food taken and the quantity of gastric juice secreted; and many other points, the true significance of which have not been recognized until the recent researches of Professor Pavlov."

Born in Lebanon, Conn., in 1785 he obtained a common school education and at the age of 21 years with "a horse and cutter, a barrel of cider and \$100 in hard-earned money" he left home and entered upon the work of teaching at Champlain, New York, where he remained for three years. In 1810 he entered upon the study of medicine as an apprentice with a preceptor at St. Albans, Vt., and received his license to practice in June, 1812, as has been already stated. In the following September he became a surgeon's mate (assistant surgeon) and received a commission from President Madison. He served during the War of 1812 and participated in several battles. In 1816 he removed to Plattsburgh and en-

gaged in general practice there until about 1820 when he re-entered the U. S. Army and was ordered to Fort Mackinac. In June, 1822, Alexis St. Martin was seen by him a few minutes after he received the wound which opened the interior of his stomach to scientific study and for many years afterwards was a source of solicitude to him. The story of Beaumont's trials with his wayward patient, his struggles and his triumphs, his disappointments and his heavy responsibilities in caring for St. Martin and his family is vividly told. The surgeon general at first gave him some assistance it is true, but the burden for the most part was borne by Beaumont alone and when an unfriendly surgeon general assumed office he was finally forced to resign from the army corps after a service of more than twenty-five years. During the remaining thirteen years of his life he lived in St. Louis and was an honored and influential citizen.

The book should be read by all who are interested in the struggles, disappointments and achievements of medical men. The author has done his work well and deserves the thanks of all physicians.

P. Blackiston's Son & Co. (Philadelphia) have just issued their pocket Visiting List for 1913, useful for the country practitioner and others. The fact that it is already in its 62d year shows how popular it is. It contains its usual tables of incompatibility, antidotes for poisons, doses, etc., and rules for treating asphyxia and apnoea. Its size is convenient and its make-up neat. Price \$1.25.

*The Practitioner's Encyclopedia of Medicine and Surgery in all their Branches.* Edited by J. KEOGH MURPHY, F.R.C.S. \$7.00. (London: Henry Frowde and Hodder & Stoughton, 1912.)

While it is fair to question the value and importance of such an encyclopedia, it is only just also to begin by complimenting the editor highly on having produced such an excellent work. The quality of the articles is remarkably good, and as a whole any future editor will have a difficult task before him if he desires to compete with this work, which is practical and simple—details of unusual surgical operations and pathological and anatomical data in the main being omitted, but otherwise the practitioner will find a general résumé of any medical subject upon which he may want information.

Almost all branches of science have their encyclopædias to-day and so it is natural that medicine should have its own, but how many doctors will really find this book useful? It is surprising the number of good text-books that are to be found in any young physician's library, and with these he can do better than with an encyclopædia. A five-foot shelf will hold almost all the text-books that are essential. Of course the price of this book makes it attractive. It would be still more useful did the authors of the various articles give a few references to standard works, for, supposing a young physician is called upon to give advice on the construction or management of a hospital, the article in the encyclopædia will give him only the elementary principles and he will want to look further and will be without a guide.

The division of articles so that there are long chapters on syphilis under both medicine and surgery makes the volume unnecessarily large. One comprehensive article on the subject could have been written by two men together, or by one alone and this reflection applies to other chapters as well.

It is to be noted that the paging of the contents is faulty; and that the index is incomplete as for instance there is no reference to enteric fever; scarlet or measles is not to be found under fever; under both typhoid and syphilis there is no reference to the main article; and none to the occurrence of fever in syphilis. There are a few illustrations in the volume which might as well have been omitted since many others of equal value find no place.

There should be more or none and this is equally true of the prescriptions which occur scattered throughout the volume without much rhyme or reason.

These imperfections do not seriously affect the value of this work and are drawn attention to merely that they may be corrected in a future edition. We welcome the encyclopædia as a thorough and trustworthy book of reference and hope Dr. Murphy's energy in putting it through will be rewarded by its meeting with a hearty welcome by the profession.

*Diagnostic and Therapeutic Technic.* By A. S. MORROW, M.D.  
\$5.00. (Philadelphia and London: W. B. Saunders & Co., 1911.)

No question should arise as to whether or not the hospital interne or practitioner should learn the technic of exploratory punctures, aspirations, and the minor surgery of medicine from experience. Certain it is that the technic of many of the diagnostic and therapeutic measures can be acquired only in a practical way. The responsibility of previous enlightenment rests with the teachers of medicine who give from their experience. However, the most experienced will find opportunity to refer to such a unique volume as Morrow's *Diagnostic and Therapeutic Technic*.

The field covered is as comprehensive as the title, and each procedure is described with most careful detail of indications and contraindications, apparatus, choice of methods, results, and possible accidents. General and local anesthesia are given one hundred pages of consideration, to which very little more could be added as to technic. Such chapters as Sphygmomanometry, Bier's Hyperemic Treatment and the Collection and Preservation of Pathological Material, seem decidedly out of place. Indeed, much has been included which would preferably be sought in publications of the eye, ear, nose and throat, gastro-intestinal, genito-urinary, and gynecological specialists.

Most helpful are the chapters upon Transfusions, Infusions, Hypodermoclysis, and Venesection. Such subjects as vaccination and administration of antidiphtheric serum are appropriately handled. In fact, throughout the book technic is very satisfactorily described in detail. In this the volume fulfills its purpose and supplies a great need. So far as I know, there is no similar effort in the over-abundant supply of medical text-books.

The illustrations are necessarily diagrammatic. Some points of value are missed. For instance, for lumbar puncture the patient is "placed upon his left side." This would be convenient for a left-handed operator, but decidedly awkward for the majority. Again, no emphasis is laid upon the all-important point of having the spine straight, so difficult to obtain in the average bed. In such a complete consideration of the subject, it seems odd that no mention is made of the great value of the simple, three-way stop-cock which may be attached to any threaded syringe, converting it into a most useful instrument for withdrawal or introduction of fluids.

Physical diagnostic methods and clinical microscopy are included, but too briefly, of course, to be of any value.

If the author had adhered strictly to the title, the volume could have been reduced one-third and brought the price perhaps within the reach of more who need the technic.

*A Practical Hand-book of the Diseases of the Ear.* By WILLIAM MILLIGAN, M.D. and WYATT WINGRAVE, M.D. Illustrated.  
\$5.00. (London: Macmillan & Co., Ltd., 1911.)

We regard this work as the best of the English text-books on diseases of the ear.

The subject matter is clearly and briefly presented. All the modern methods of diagnosis and treatment are mentioned, together with references to the more important original articles.

The value of the book is greatly enhanced by the chapter by J. Purves Stewart, on Diseases of the Ear in Relation to General Medicine. This chapter contains a brief, concise summary of the lesions of the nervous system which produce auditory disturbances together with a description of the more striking auditory phenomena which form a part of the clinical picture.

The treatment of the nose and naso-pharyngeal mucosa is very properly insisted upon (page 194), and the authors have greatly added to the value of the work by giving, in Chapters XL-XLIV, an admirable resumé of the conditions of the throat, nose, and naso-pharynx which may be primarily responsible for otological diseases.

The suppurative otological diseases, with their complications and sequelæ, are discussed in detail, and quite properly so, since the recognition and treatment of such conditions is of the greatest importance to practitioners and surgeons alike.

Dr. Milligan has made tuberculosis of the middle ear and temporal bone one of his special studies, and the chapter on this subject forms a valuable monograph.

The book is particularly attractive because it is something more than a mere "rehash" of other text-books and manuals; it contains a large amount of original work and many references for those wishing further information.

*A Treatise on Pellagra for the General Practitioner.* By EDWARD JENNER WOOD, M.D. Illustrated. (New York and London: D. Appleton and Company.)

There is to-day no reason why physicians in this country should not have a clear mental picture of this disease, even though they may have met with no cases. In addition to the translation of Marie's work, both Roberts and Niles have written treatises on Pellagra, and now Wood adds his to the series. There are also valuable reports from some of the southern states' boards of health, and numerous articles in the current literature which are of avail to the student interested in this new American problem. The disease is a far reaching one and while most prevalent in the south, yet sporadic cases are turning up all through the United States. Until we know the cause of this disease it is all important that these cases should be recognized, for if they are due to some organism the patients must be most carefully watched as they may prove to be carriers of disease which like malaria may be transmitted through the bite of some insect. If, however, the malady is due to some chemical process it will not be necessary to isolate these patients. Wood is a supporter of this newer theory of infection, rather than the older one which holds that the disease is due to mouldy corn. But the proof that the bite of a fly is accountable for pellagra is, as yet, far from convincing; and it will require the continued work of many students of the problem before the obscure cause is finally found. Dr. Wood has written an interesting work, illustrated by some excellent photographs; his presentation of the disease in its various forms is thorough and his monograph will, it is certain, remain for some time the standard work in English; but the other works referred to all have points of excellence and are needed for a completer study of the entire question.

*The Surgical Clinics of John B. Murphy, M.D.* October, 1912.  
Vol. I, No. 5. (Philadelphia and London: W. B. Saunders Company.)

There are eighteen different surgical subjects discussed in this number. Such talks as these at the operating table prevent a subject from being treated in a thorough manner, but they often bring out points, which are important and which are frequently overlooked in a more carefully prepared lecture as being trivial. It is from this point of view that students will find the reading of these clinics interesting.

*The History of the Prison Psychoses.* By DRs. PAUL NISCHÉ and KARL WILLIAMS. Translated by FRANCIS M. BARNES, JR., M. D. and BERNARD GLUEK, M. D. (New York: The Journal of Nervous and Mental Disease Publishing Company, 1912.)

This is the latest monograph of the important series published by the above named company, and is an interesting survey of the development of the modern German views on prison psychoses. Prison physicians and others called to examine persons detained in our station houses and jails will find this historical review an aid in determining how best to classify some poor mentally impaired prisoner. The translation has been well done.

*The Care of the Body.* By R. S. WOODWORTH. \$1.50. (New York: The Macmillan Company, 1912.)

Mr. Woodworth's book is written as a guide on personal hygiene for young men, and is well adapted to its end. The instruction given is simple, and can be easily comprehended by any intelligent youth although he has not studied medicine. It may be safely recommended, and will be of real service in schools and elsewhere. To-day more than ever before the public is being educated in all matters relating to health, and such a book as this will help to advance the good work that is being done along these lines.

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# BULLETIN

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## THE HISTORIC EVOLUTION OF VARIOLATION.\*†

By ARNOLD C. KLEBS, M. D., Lausanne, Switzerland.

Immunology, the latest child of medical science, has reached, after a short existence, a very considerable development, some even think maturity. However true this may be, its creation has certainly called forth efforts of the most varied nature embracing and mobilizing almost all branches of physical sciences. The very acuteness of these efforts is inimical to retrospection. Only very recently some experimenters have searched the earlier literature, of vaccination for instance,<sup>1</sup> for support of their conception. Variolation has entered very little, if at all, into such investigations and it is really astonishing how thoroughly it is forgotten, this most interesting epoch in medical history, which kept greater and humbler minds in fever heat during almost one whole century. This oblivion is particularly curious because variolation called forth a unique and extensive trial of a specific preventive method, the logical consequence of which was vaccination. This fact does not detract from the merits of Jenner, who by observation and conclusive experiment was enabled to render an immortal service. It is true that Jenner was unaware of the generic identity of vaccinia and variola, that to him cowpox was a disease *sui generis*, the inoculation of which conferred im-

munity to smallpox for some unknown mysterious reason. It is this conception which stamped vaccination as a new departure and it is largely responsible for the oblivion into which variolation has fallen. Jenner's belief<sup>2</sup> in the common derivation of cowpox and smallpox from the grease of horses, and Pearson's and Baron's vague suspicions of a more intimate relationship between variola and vaccinia, passed unnoticed for almost another century, after which the intrinsic analogy of variolation and vaccination could be demonstrated.

In searching for the earliest origins of variolation I may cite the words of Sir George Baker,<sup>3</sup> one of the most scientific inoculators of his time: "It cannot but be acknowledged that the art of Medicine has, in several instances, been greatly indebted to accident and that some of its most valuable improvements have been received from the hands of Ignorance and Barbarism." This indebtedness to the intuitive genius of popular reason and procedure is strikingly illustrated in the reports of early practice of variolation. While the learned since oldest times strained every effort towards the discovery of a Medicinal antidote, the simple-minded evolved the idea of protective inoculation. It is difficult to ascertain any one locality where variolation was first practised. From its wide distribution it would seem that it arose spontaneously in various places where the need for it occurred. The earliest alleged reference to variolation in the chronicles of the 6th century by Marius, Bishop of Avenches, I have been unable to verify.<sup>4</sup> I found only the well known report of a deadly

\* Authors in 18th century literature speak only of "inoculation" (grafting, insertion). At present for the sake of clearness the term "variolation" seems preferable. In retrospective reviews of the subject the term vaccination is often used erroneously for variolation and a similar confusion is likely to occur if modern writers persist in using faultily the words "vaccine and vaccination" for protective and therapeutic inoculation generally.

† Paper read before The Johns Hopkins Hospital Historical Club, October 14, 1912.

<sup>1</sup> von Pirquet, *op. cit.*, introduction.

<sup>2</sup> Jenner, *Inquiry*, 1798, 3d paragraph.

<sup>3</sup> G. Baker, *An inquiry*, etc., 1766, p. 1.

<sup>4</sup> Edit. Bouquet, *Histoire des Gaules*, II, 12.

epidemic (570 and 571 A. D.) in Italy and Gaul of a disease which for the first time is called "variola." Clearly referring to variolation is a remarkable verse of the School of Salerno\* (10th or 11th century) entitled *adversus variola* and which runs as follows:

*Ne pariant teneris variolae funera natis  
Illorum venis variolas mitte salubres.  
Seu potius morbi contagia tangere vitent  
Aegrum aegrique halitus, velamina, lintea, vestes  
Ipseque quae tetigit male pura corpora dextra.*

For preventive purposes the voluntary transference of a benign variola is surely recommended here, the *venis*, however, may indicate "system" generally, in which case the disease is to be transmitted by simple exposure or we may take it more literally and an operation then suggests itself. The last three lines giving preference in very modern-sounding language to the avoidance of infection by contact, seems to me to lend strength to the latter interpretation.

The first authentic reports of this practice we find in the Ephemerides of the Academia Cæsarea Leopoldino-Carolina published at Leipzig between 1670 and 1705. Here Dr. Vollgnad of Breslau\* in 1671 and Dr. Schultz of Thorn in 1677 clearly report instances of the custom of "buying the smallpox." There is, however, no reference made to the actual inoculation with the pock scabs purchased in the plague house, but that such was done is very likely, since Schultz speaks of the rather serious illness which his own brother acquired in this manner. It does not seem to me that these cases have anything to do with the sympathetic transference of disease, which agitated some medical minds of the day, and as instances of which they obviously were reported. Creighton\* gives an interesting example of this form of transplantation in 1657: "Some persons in the smallpox keep a sheep or a wether beside them in the chamber, those animals being apt to receive the envenomed matter and draw it to themselves"—only a slight modification of the Jewish scape-goat! Of course this has as little to do with variolation as the Biblical passage cited by Massey in 1722 in condemnation of inoculation: "So went Satan forth from the presence of the Lord and smote Job with sore boils from the soles of his feet unto his crown" (Job, II, 7).

\* Smallpox is hereby not defined with any certainty. Its root *varus* as used by Celsus and Pliny is meant to indicate a pustulous disease, especially of the face.

\* S. de Renzi, *Flos Medicinæ Scholæ Salerni*, Naples 1859, p. 90 (3059, *et seq.*). A footnote of the editor gives as his opinion that the first two lines refer to variolation, which was not invented in the 18th century, or in Greece, but is older.

\* This may be rendered: In order that variola may not produce death among tender babes, put into their veins a favorable variola. Better still they should avoid touching the contagium of the disease: the sick person, the breath of the sick, the clothes, the coverings, the garments and such clean bodies as he may have infected (*tetigit male*) with his hand.

\* H. Vollgnad (1634-1682), member of Academy, 1669.

\* Slatholm (Buntingford), 1657, cited in Creighton, *History of Epidemics in Britain*, p. 475.

Further reports of the ancient practice all date from the time of the medical introduction of variolation to Europe and America. They were of the usual order, meant to show that there is nothing new under the sun and some of them, therefore, have to be taken with caution. Thus we hear of a crude variolation in Scotland (Monro I, & Kennedy), in Wales (Perrot Williams),<sup>10</sup> in Auvergne and Perigord (de la Condamine), in Jutland (Bartholin), in the Duchy of Cleve (Schwencke) and other parts of Germany. Of the inoculations practised in Greece, whence it was introduced to Western Europe by way of Constantinople, I shall speak later. The earliest traces of variolation are found in Asia and in Africa. In Africa the practice continues to this day among certain tribes, chiefly negroes, in the eastern, central and western regions. On the White Nile in the equatorial province (Welson & Felkin) among the Bari, and further east among the Somali (Stahlmann) a similar custom is found. It seems to have been highly developed by the most important of the native Bantu tribes, the Baganda, living northwest of Lake Victoria in the old Kingdom of Uganda. Further west we find the Wanjamwesi, and in the Sudan the Ashanti, and some Moorish tribes practice inoculation on their children. From northern Africa we have the report of the Tripolitan Ambassador, Kassam Aga, which made the round of 18th century literature, about the ancient variolation by Mohammedan tribes in Tripolis, Tunis and the Kabyl mountains. Not long ago we had a verification of this latter report by a French naval physician, Dr. H. Gros,<sup>11</sup> stationed at Rébéal in Algeria. He has observed a considerable number of variolations practised by Arabs and Kabyles and curiously enough comes to the conclusion that variolation ought to be resorted to if, for some reason or other, the supply of vaccine became exhausted. This account contains many interesting observations which corroborate most of the historical records of the 18th century.<sup>12</sup>

Exceedingly interesting accounts about smallpox inoculations are available from Asia. I can only briefly refer to them. China, of course, again is said to have known variolation since remotest times. We have no reliable data as to the age and extent of the practice; we must be satisfied with the knowledge that a method of inoculating the virus into the skin or in the form of dry powder blown into the nostrils, has been known to exist before it reached Europe.<sup>13</sup> In India a similar method seems to have been carried out on a systematic plan by special delegates of the Brahmin caste in conjunction with a religious cult of the smallpox deity.<sup>14</sup>

<sup>10</sup> Philos. Transact., 1722.

<sup>11</sup> La variolisation, Janus, 1902, VII, 169.

<sup>12</sup> Other reports from travellers about variolation: Bruce (1790), Levaillant (1790-1796), Michaux (ab. 1800) for Africa, Cook (ab. 1780) for Senegambia, Barbary, Bengal.

<sup>13</sup> The "Tchan-teou" or "sowing the smallpox" in d'Entrecolles, *Lettres édif. et cur. des missions* 1726, XX, 34 (from Pekin) and other reports in *cit. letters*.

<sup>14</sup> Holwell, *op. cit.* Also J. Moore, *History of the Smallpox*, Lond., 1815, 26-34, with plate representing the religious rite, from a Hindu drawing in the library of Mrs. Bliss of Kensington.

None of these primitive variolations served to acquaint Western Europe with the practice. Only after it had reached a certain development in Constantinople could it be studied, reported and recommended. From this city Lady Mary Wortley Montagu, wife of the British Ambassador to the Porte, wrote to her friends at home about the method of inoculation as practised under her eyes and expressed her intention (to Sarah Chiswell, April 1, 1717, from Adrianople) of introducing it to England. She even caused the inoculation of her three-year old son Edward, by a Greek woman with Maitland's assistance,<sup>22</sup> and influenced that of the three children of the Marquis de Châteauneuf, Secretary to the French Embassy at about the same time (1718). Her inspiration and these examples undoubtedly opened the doors for the introduction of the practice in England. There was already some medical agitation on the subject, before Lady Mary became interested, and it can safely be presumed that she was not ignorant of it. Dr. Timoni, a Greek physician of Constantinople educated at Oxford, published in 1713 an account of the method of variolation as observed and practised by him. In December of the same year he sent a personal communication on the subject to Dr. Woodward,<sup>23</sup> who read it before the Royal Society. A little earlier a similar report reached the Swedes, sent to them from Bender in Bessarabia by their exiled king, Charles XII, with the recommendation to introduce the method.<sup>24</sup>

Other medical men in England at this time had some personal knowledge of the method which they had seen practised in Constantinople. We know of two, a Dr. Terry of Enfield, who later is consulted about it by Sir Hans Sloane, and a Scotch surgeon, Peter Kennedy,<sup>25</sup> who describes the method in his book in 1715. A dissertation on inoculation appears in Venice by a Dr. Pylarini<sup>26</sup> the next year. A friend and former consular colleague of the latter in Smyrna, Dr. Wm. Sherard, informs Sir Hans Sloane and, through him, the Royal Society, of this publication with details about the method and an account of Dr. Pylarini's experiences. Now the Royal Society becomes really interested and the pages of the Philosophical Transactions of the following years are filled with further accounts, which Douglass of Boston later (1730) characterizes sneeringly as "virtuoso amusements."

At the same time something was heard of the "Greek

method" in France. Boyer<sup>27</sup> of Montpellier, later Dean of the Medical Faculty of Paris (1756), had travelled as a young man in the Orient and had there become acquainted with variolation. On his return to Montpellier he studied medicine and wrote his inaugural thesis (1717) on inoculation and the reasons why it might be imitated to great advantage in France. Actual inoculations very probably were practised in Paris at about this time by a Greek physician Carazza. Eller tells us of making his acquaintance there, and how he was taught the method and how he successfully inoculated a child. Although Eller does not mention the exact date, it is evident that it took place in or before 1720, because in that year he went with Lord Peterborough to England and returned from there to Germany in January 1721.<sup>28</sup>

At this moment, when the new method knocked at the doors of the universities, promising fresh hopes but also planting the first seeds of discord among the sister faculties, the 18th century is yet young. The glaring contrasts and contradictions are not as apparent as they will become later, the genius of Newton—he still presides over the Royal Society—is only beginning to assert itself. In medicine Sydenham's influence is paramount, while Boerhaave in Leyden and Morgagni in Padua are training men who are to found modern medical science. Hoffmann and Stahl supply the cravings for theoretical contemplation, while practice continues on old lines. Everywhere reform is in the air, the struggle against superstition and for tolerance has begun. The realization that the riddles of life and its problems are not to be solved by pure metaphysical speculation begins to dawn upon the learned and experiment is more and more resorted to for the final criterion.

From the time of its introduction to the Occident in 1713 to the advent of vaccination in 1798 and its general acceptance in 1840, variolation does not follow a course of steady progress. As we shall see, it enjoys a few years of the success of novelty (until 1727), followed by twenty years (1746) of indifference, after which it slowly gives rise to a remarkable period of serious scientific investigation.

The honors of the first inoculation in the Occident (excepting that by Eller in Paris) will probably best be divided between London and Boston. Dr. Fitz, in an admirable account of the early inoculations in Boston, tends to the belief that Boylston, inspired by Cotton Mather, made his first attempt

<sup>22</sup> Letter to Lord Montagu (of March 23, 1718) at Pera from Belgrad.

<sup>23</sup> John Woodward (1665-1728) excellent geologist, but poor physician. See Creighton's (*op. cit.*, p. 449) amusing account of his duel with Mead in Gresham College where he was professor of physic. Its cause, the smallpox controversy, involved also Friend and later Dover. In 1718 he published a tract "the State of Physick" in which he discussed the "new practice of purging" in smallpox.

<sup>24</sup> This report was probably written by the king's physician, Skraggenstyerna.

<sup>25</sup> Peter Kennedy: Essay on external remedies (Chap. 37), 1715.

<sup>26</sup> Pylarini, Nova et tuta, etc., 1715. Sloane in Phil. Trans., XXIX, 1716.

<sup>27</sup> J. B. N. Boyer, 1693-1768.

<sup>28</sup> J. Th. Eller, *Observationes cognoscendis et curandis morbis praesertim acutis*, Regimont. & Lips, 1762, p. 150. (French transl. Par. 1774.) Eller was born in the Duchy of Anhalt in 1689, became M. D. in 1716 then travelled in Holland and practised in the mines of the Harz Mountains. From here he went to Paris and worked under Hecquet, Astruc, Helvetius and Winslow, giving much attention to surgery, at the Hôtel Dieu and the Salpêtrière. In London he frequented Cheselden, Mead, Sloane and Newton. He left London in January, 1721, became court physician in Anhalt, inoculated several persons, and in 1724 he was at the court of Berlin, teaching at the newly founded Medico-Surgical College. He and Stahl (Halle) are largely responsible for the sanitary reform in Prussia, which formed the basis for the present institutions.



without knowing of the inoculations performed in London.<sup>22</sup> There is no direct evidence of his ignorance and he certainly had time to learn about the London inoculations in April and May, since he inoculated his son Thomas and the two slaves on June 26. Undoubtedly he had courage enough to proceed without any other assurance than that of his friends and the older reports at hand, but the situation was precarious and it looks as if the latest news may have been welcome and actually determined him.

The merits of Lady Montagu in inciting the early trials in London were undoubtedly great in that year of 1721, when the smallpox was raging on both sides of the Atlantic. A Portuguese physician in London, à Castro, had anonymously published a pamphlet on the subject in March and Dr. Walter Harris spoke recommendingly of inoculation before the College of Physicians on April 17. Lady Mary probably did not need these learned suggestions to remind her of her experience in the Orient and with the danger of smallpox at the door, she had Maitland inoculate, in April, her four-year old daughter, the future Lady Bute. One of the three interested spectators from the College of Physicians, Dr. Keith, was sufficiently impressed by the harmlessness of the operation to have his own six-year old son inoculated on May 11. In this case, bleeding was resorted to as a preparatory measure and we see herein, as also in similar examples in Boston, the germ of that "preparation" which is to play such an important rôle later on. Lady Mary meanwhile does not stop with the inoculation of her own child; she takes up the personal propaganda begun in her letters from the Orient, she finds it now easy to induce many of her friends to follow her example, but her main efforts she exerts towards winning the court. In this task she is aided by her intimate relationship with the Princess of Wales, later Queen Caroline, whom Voltaire, because of her intelligent interest in arts and sciences, addresses as the "philosopher on the throne." George I is willing to permit the inoculation of his grandchildren but a preliminary experiment is deemed advisable. Here is the first beginning of scientific procedure. Six condemned criminals in Newgate prison are inoculated as test cases, the best medical men of London are watching the experiment, with Mead at their head. Nothing unusual happens; somewhat severe symptoms are observed only in one girl, whom Mead inoculated with dried virus in the nostrils (Chinese method), but she also recovers. One man in whom the inoculation did not "take," is found to have had smallpox before. A further test is made by Mead and Steigenthal, who send one of the inoculated patients to Hertford where a severe epidemic rages; no infection takes place. George I and his court feel reassured by the results of these experiments, and further good reports having reached the town from Halifax, in Yorkshire, where Nettleton had

inoculated with satisfactory results since December, the operations on the Princesses Amelia and Caroline take place on April 19, 1722. The surgeon Amyand, attended by Sir Hans Sloane, Teissier and Maitland, performs the inoculation.<sup>23</sup> The immediate result of this evident approval of variolation by the court was that the nobility hastened to follow the august example and so we find the gazettes reporting on these events, mentioning all the names of the ultra-fashionables. The next result was the formation of two opposing factions. Pamphlets were written, sermons preached for and against the new method, mostly by people who knew nothing or next to nothing about inoculation. This condition continues through the whole epoch of variolation and as a matter of fact long after its abandonment. In the vast literature thereby produced it is often exceedingly difficult to find one's way. Wagstaff, the medical satirist, Blackmore, inferior medical author and poet, Clinch, the surgeon, Massey, the apothecary of Christ Hospital, are the chief opponents; the learned Dr. Freind<sup>24</sup> wavers, but objects to the noise made about inoculation, Arbuthnot, friend of Pope and Swift and commentator of Boerhaave, Jurin, secretary of the Royal Society under Newton, Mead and Sloane were, however, more or less active in the recommendation of inoculation.

The arguments brought forth against variolation were, its risks to the individual, the uncertainty of its protective power and the danger of its spreading the disease. The last argument had received support when the news came of an accident that had happened in Maitland's experience at Hertford, where he had gone to inoculate in the autumn of 1721. A child ill with artificial smallpox had infected six servants of whom one had died. This demonstration of the contagiousness of inoculated smallpox offered the strongest point to the cause of the opponents. They, however, resorted oftenest to personal vituperation or bitter condemnation on religious and moral grounds. On the other hand the inoculators and their upholders, although reiterating the most obvious advantages of inoculation, viz., freedom in the selection of appropriate subjects (children), favorable external circumstances (seasons), and careful preparation, resorted almost exclusively to statistical data in their support. Jurin,<sup>25</sup> who excelled in mathematics, soon collected enough cases to figure out the ratios as: One death only in 91 inoculated (two in 182), while the natural smallpox killed one in five or six. He refers to the "letter of Cotton Mather of the 10. March 1721"<sup>26</sup> in which five to six deaths are reported among 300 inoculations, mak-

<sup>22</sup> A medal was struck to celebrate the event. *Av. George I, 1721, Rev. Inoculation instituted.* (Pfeiffer, 373a.)

<sup>23</sup> See reference to John Gaddesden in his "History" (1725): had he "lived in our day, he would, I don't question, have been at the head of the inoculators." (Creighton II, 478.)

<sup>24</sup> Jurin to Cotesworth 1723. James Jurin born 1684, secretary and later president of Royal Society, was one of the first physicians to Guy's Hospital. The advocacy of his "lixivium lithontripticum" brought him questionable fame.

<sup>25</sup> A. L. (contemporary copy) in Sloane MSS. 3324, fol. 260 (see Kittredge, *op. cit.*, p. 477). The letter is also quoted by Douglass in his "dissertation" of 1730.

<sup>26</sup> Professor Kittredge (*op. cit.*) has recently given valuable additional information on the subject of early variolation in Boston. It leads to the conclusion that Cotton Mather's knowledge of it has not been fully recognized and especially that he was acquainted with variolation (among negroes) before he received the reports about it from Europe.

ing a ratio of one in 60. He concludes from it that inoculations in New England were less careful.<sup>27</sup>

The technique meanwhile had seen considerable deviations from its primitive Greek prototype. In Constantinople, Maitland had already replaced the dirty needle of the woman operator by the lancet. Nettleton, who probably had the largest experience in these early years, thought it important to make rather deep incisions and to keep them open so that the wound would drain freely and allow the morbid humors to escape. The arms or thighs were the favorite regions chosen.<sup>28</sup> The virus was taken directly from a smallpox patient and transferred, or it was collected on threads and dried for later use.

It seems that the inoculations were not often performed by the physicians themselves; they usually had a surgeon do it and watched the case before and after. Thus a type of inoculation specialist was evolved and all sorts of people took it up as a lucrative profession.<sup>29</sup> Some of the failures may easily be attributed to crude methods. Maitland seems to have created the type of the itinerant inoculator, whom we can soon follow all over Europe. We have already encountered Maitland in Hertford; a few years afterwards he is on the continent inoculating Prince Frederick and others at Hanover. After this we find him in Scotland<sup>30</sup> where he has ill-luck, losing one in ten. This experience, the Hertford case, and the deaths of several prominent persons, duly registered in the gazettes, added powerfully to the arguments of the opponents. The subject was brought up in Parliament and inoculation declared dangerous. This was in 1728. Up to that year Jurin<sup>31</sup> could collect in his report 897 known inoculations with 17 deaths, not all directly attributable to the operation. He considered the practice now "exploded," while the otherwise sceptical Douglass<sup>32</sup> admits that the opponents are now prepared to acknowledge that "inoculation, generally speaking, is a more easy way of undergoing smallpox."

The Continent, meanwhile, did hardly more than act the part of the spectator. LeDuc of Constantinople writes the first inaugural thesis on inoculation at Leyden; it is approved on July 28, 1721, and published together with the dissertations of à Castro and Walter Harris of London in 1722. Boerhaave maintained an expectant attitude. We have no reports of his having tried the method himself or persuaded others to do so. Theoretically he surely approved, for we find him saying at the end of his Aphorism 1403 (Edit.,

<sup>27</sup> The figures of Cotton Mather are quoted by the anti-inoculists again and again with considerable success all over Europe.

<sup>28</sup> In the Greek practice the forehead, shoulders, hands and other parts of the body were chosen, the choice being determined on religious grounds and it varied with individual inoculators.

<sup>29</sup> We know of a blacksmith who thus changed his occupation, and a man-servant who gave notice to his employer because he could earn more as an inoculator. (Watts, Watson.)

<sup>30</sup> Alex. Monro I, 1697-1767.

<sup>31</sup> See also Scheuchzer (son of the Zurich naturalist) on success in Great Britain, 1729. Another late endorser of the method was Lobb in 1831. (His treatise on smallpox received the praise of Boerhaave.)

<sup>32</sup> Douglass, 1730, *op. cit.*

Leyd., 1727). *Prophylaxis insitiva videtur satis certa tutaque.* Of his pupils Van Swieten continues in this reserved attitude, while de Haën becomes one of its most persistent opponents and Tronchin one of the most famous inoculators in Europe.

In Germany Eller, whom we have met already in Paris, has returned to his home in Anhalt. As physician to the local court he performs two inoculations, but, soon called to the Prussian court, he is not allowed to see smallpox cases and has to desist. In Breslau reports are received of inoculations performed by one Reimarus in Hungary.<sup>33</sup> In the two universities, Altdorf and Erfurt, which have long ceased to exist, doctor dissertations are published on inoculation by Müllich and Cramer,<sup>34</sup> but they report no new trials. In Hanover, however, the inoculation of Prince Frederick acted as a stimulant. J. E. Wreden publishes a treatise on it and his son John, later body surgeon to the Prince of Wales, soon begins to inoculate.<sup>35</sup> Outside of the Electorate of Hanover, naturally influenced by England, Germany contributes very little to the history of inoculation. Of Austria, Italy and Switzerland I shall speak later. In Sweden we have one publication in 1737 by Spöering, but also no actual inoculation.

The history of variolation in France offers much of interest and forms a valuable contribution to the annals of culture in general. At the time when variolation first appeared in England, medical science and practice in France had made little progress since the days of Ambroise Paré and Guy Patin. Montpellier showed more signs of progressive activity and in later years especially, the children of this Alma Mater were prominent in the ensuing struggle. While in England inoculation occupied minds rather intensely for eight years, only in the one year of 1723 is this subject at all considered in France, particularly in Paris, and then only academically. Louis XV was then thirteen years old and the Duke of Orleans was nearing the end of his regency and his life. Dr. de la Coste, an enthusiast for inoculation, who had followed its introduction to England, writes about it to Dodart,<sup>36</sup> formerly physician to Louis XIV. He tells him all he knows about the subject and especially that the English court is in favor of it. At a solemn meeting at the Sorbonne he explains to the learned dean and nine doctors the evident advantages of inoculation. After a careful analysis of the moral and religious factors involved, it was decided that experiments might be made without interfering seriously with Divine providence. This meeting had the effect of winning over the Regent, who also probably was influenced favorably by Helvetius<sup>37</sup> who was close to him at the time. It therefore looked for a while as if experiments might begin. Then appeared an anonymous pamphlet entitled: *Raisons de doute contre l'inoculation*, in which strong language was used against *la méthode anglaise* and its promoters. It

<sup>33</sup> Breslauer Versuche, XVII, 253.

<sup>34</sup> 1725 and 1726.

<sup>35</sup> Report in 1739, London.

<sup>36</sup> Cl. J. B. Dodart, 1664-1730.

<sup>37</sup> J. Cl. Adr. Helvetius, 1685-1755.



was soon learned that the author was old Hecquet,<sup>38</sup> dean of the *Faculté de médecine*, more theologian than physician and a stubborn opponent of all innovations. His words carried much weight and when the Regent died on December 3, the chance of inoculation grew very faint and was entirely extinguished at a meeting in the *École de Médecine* on December 30<sup>39</sup> where the *questio medica*, worded ominously "Is it a crime to inoculate?" was discussed under the presidency of Claude de la Vigne,<sup>40</sup> the new king's new physician. An interesting contrast: the Sorbonne for, the *École de Médecine* against the new method! As a child Louis XV comes to power; he was of course not to blame in that, for 30 years after his advent, inoculation was hardly mentioned in France, but curiously enough, as a man, after 50 years of a disastrous reign, he falls victim to the very disease the method was intended to prevent. Voltaire, in his apartment quite close to the *École de Médecine*, at this moment is making a very personal and most unpleasant acquaintance with smallpox, nursed by his devoted friend Adrienne Lecouvreur. Two or three years hence he is to begin his eloquent propaganda for inoculation in one of his letters from that England which is to influence so strongly his whole point of view.

During the 20 years following the practical abandonment of inoculation in England, and while next to nothing was done in Europe, events occur in America which later are to help considerably towards a revival of the practice. An epidemic of smallpox in Charleston in 1738 gives the incentive. A surgeon, Mowbray, and a Scotch physician, Kilpatrick (later as Kirkpatrick one of the foremost inoculators in England), inoculate a very considerable number of persons in that year.<sup>41</sup> Mowbray evidently started the inoculations and seems to have done the greatest number. Kilpatrick's account, which was published first in Charleston and then in London in 1743, relates, with great frankness, the successes and failures (about 800 inoculations with eight deaths).<sup>42</sup> They met with distinct opposition, especially on the part of other practitioners.<sup>43</sup> Kilpatrick, in theory, favors careful preparation of the patient before the operation. His guiding principle is the cooling regimen of Sydenham with a "few remedies perhaps" so that the "Solids and Fluids may be reduced from a greater, to less Inflammability." His conception, as these quotations show, is that of his time but he admits, "without prejudice, that preparation was too often neglected with us." We also learn from him, and this is an important innovation, that Mowbray very often inoculated with the virus taken from the pustules of a previous inoculation and that he repeated the process up to six times,<sup>44</sup> without perceiving any reduction of virulence. It would be inter-

esting to enter more fully into the excellent observations of this essay. They are distinctly in advance of the time and I believe mark a more valuable advance in the history of inoculation in America than that presented in a pamphlet of Dr. Adam Thomson, published eight years later and of which Dr. Henry Lee Smith<sup>45</sup> has given a full account. From this "discourse" of Thomson's it appears that he had begun to inoculate in Philadelphia at about the same time when Mowbray and Kilpatrick started their experiments in Charleston. The crux of his method is specific preparation, applying Boerhaave's suggestion that mercury and antimony may act as preventives against smallpox. He lays greater stress on these medicines than does Kilpatrick, otherwise there is no difference between the two methods. There is no doubt that Thomson succeeded in impressing his patients and also some doctors with his method of preparation. Dr. Gale of Connecticut seems to have been his most enthusiastic follower. At least I find him writing to Huxham<sup>46</sup> about it: Boerhaave's "intimation was improved, and mercury introduced into practice, by physicians in the English American Colonies, about 1745. Several American physicians claim the second glory of Boerhaave; perhaps Dr. Thomas (*sic.*) of Virginia, and Dr. Murison of Long Island." Ruston<sup>47</sup> a little later in speaking of this method ascribes it, as does Gale, to Murison and to Dr. Thomson of Virginia. Ruston who is in favor of a mild preparation, shies at this particular one for the secret of which, he says, "considerable premiums were offered." Ten to twenty grains of calomel every other night counteracted by a drastic purgative for two weeks seem to him rather violent as a preparation for more trouble!

We are now nearing the middle of the 18th century. The failures of the introductory period in England were almost forgotten and Europe in general was becoming more and more receptive to such an innovation and, with the increasing restlessness of the age, receptiveness developed into eagerness. In England Kilpatrick's essay (1743) on the experience in South Carolina was very largely responsible for a revival. He had arrived himself and at once set to work as a specialist inoculator. Among those who followed his example are Ranby, Middleton, Hawkins, Frewen, Burges, Archer, etc. The alleged necessity of an elaborate course of preparation on hygienic and medicinal lines, of a surgical operation requiring often a prolonged after-treatment, held out golden promises to physician, surgeon and apothecary. Mercenary calculation therefore entered very largely into the advocacy of "preparation" and deep incisions. It is well to bear this in mind. Some of the more earnest practitioners object to these complications but, in spite of them, this cumbersome procedure maintains its vogue during the following 20 years. The fact that it is very costly rather increases the demand for it among the wealthy and thus it gains influential protectors. This leads to provision for the poor and here the foundation, under the patronage of the Duke of Marlborough,

<sup>38</sup> Phil. Hecquet, 1661-1731.

<sup>39</sup> Duvrac's account, 1755.

<sup>40</sup> Cl. de la Vigne de Frécheville, 1695-1758.

<sup>41</sup> Kilpatrick, *op. cit.*, p. 44. On May 21, 1738, the first three persons were inoculated in Charleston, the two daughters of a Mrs. Sarah Blakeway and a Miss Baker.

<sup>42</sup> Kilpatrick, *op. cit.*, p. 34.

<sup>43</sup> Kilpatrick, *op. cit.*, p. 44, controversy with Dr. Thomas Dale.

<sup>44</sup> Kilpatrick, *op. cit.*, pp. 49 and 50.

<sup>45</sup> Johns Hopkins Hosp. Bull., 1909, XX, 49.

<sup>46</sup> John Andrew, 1765, *op. cit.*, pp. 9 and 44.

<sup>47</sup> Thomas Ruston, *op. cit.*, p. 2.



of the Middlesex County Hospital for smallpox, and soon afterwards that of others in London," marks an epoch. There was little effort made, at least at first, to utilize these institutions for a scientific study and an improvement of variolation. As each patient, because of the preparation before inoculation, had to stay a very long time, at least while a preparatory period was thought to be necessary, the benefit which the poor derived from these hospitals was very small, because of the few that could be admitted.

The practice of variolation, thus taken up in all earnest by energetic medical men, prevailed in spite of the opposition which continued unabated. The cause found a very valuable champion in Isaac Maddox, Bishop of Worcester, who in his sermons intelligently and forcefully recommended inoculation. Another churchman, de la Faye, on the other hand, used the pulpit for the fiercest denunciation of inoculation and inoculators. In medical circles all the questions involving smallpox and variolation were ventilated. The war of pamphlets is opened by a letter of one Dod Pierce to Pierce Dod, physician of St. Bartholomew and author of "Several cases in physic."<sup>48</sup>

In 1747 Mead's *de variolis* (with the translation of Rhazes' commentary) appears. He devotes a brief chapter (V) to inoculation. He is decidedly in favor of it and does not know of relapses after it. According to him the great advantage of the inoculated disease over the natural one is the opportunity afforded of selecting appropriate subjects and preparing them "by drawing away, where necessary, some blood, and gently purging the humors," in order to "obviate the violence of the approaching fever." He cannot imagine much benefit from the discharge of the wound of inoculation and in general finds the artificial disease so mild that it hardly calls for help from any physician. This common-sense point of view was not shared by the majority of inoculators, in whose interest it was to emphasize the importance and gravity of the operation. But Mead's great influence and authority helps to smooth the path for the method. And indeed, all through the following years and considerably into the 19th

<sup>48</sup> This hospital changed its location several times shortly after its opening in Windmill Street, to Mortimer Street and finally to Lower Street, Islington. The other hospital soon after opened at Bethnal Green (44 beds). After 1750 15 patients could be received, prepared and inoculated at the Inoculation Hospital in Old Street, St. Luke's, whence they were taken for after-treatment to the hospital at Fray Lane. In 1752 the governors of Charity opened another large smallpox hospital at Coldbath Fields (130 beds) also for preparation previous to inoculation.

<sup>49</sup> "I do not find this delightful biting satire mentioned in any history of inoculation and it well deserves notice as it gives an invaluable picture of the manner of thought among certain physicians of the day. The author, it may well be Kirkpatrick, pretends that he is trying to expose "the low Absurdity, or Malice, of a late spurious Pamphlet, falsely ascribed" to Dr. Dod, and aims particularly at his principal case in physic: "giving an account of a person who was inoculated for the smallpox, and had the smallpox on the inoculation, and yet had it again." With banter and derision, jeering and sarcasm, he parodies Dod's bungling, awkward language, denounces his absurd reasonings and faulty observations. (In the Surgeon-General's Catalogue the author is given as W. Barrowby.)

century, we see variolation in England in continual progress. I need not enter into the details of its historic evolution here, since this has been admirably done by Creighton. It may be sufficient to point out that in the first 20 years of the revival, during which the method was exploited by more or less unscrupulous practitioners as a lucrative occupation, we do not find many evidences of a scientific improvement. In Kirkpatrick, Mead and Frewen we can already observe attempts at simplification and a desire for a better understanding of the fundamental questions involved. But it is only after 1764 with the advent of Gatti, the Suttons, Dimsdale, Watson, Mudge, Maty, Lettsom and others that a more scientific, systematic spirit is infused into the growing movement.

The tendency now becomes manifest to "prepare" chiefly by hygienic and dietetic means and to abandon frequent bleedings and violent purgation. The Suttons<sup>50</sup> have certainly a great share in the vulgarization of this practice. The mystery with which they surrounded their method and their successful avoidance of accidents were powerful factors in their favor. Their hygiene consisted mainly in a continuous open-air life before inoculation and during convalescence, to which were joined cold water applications. The secret remedies which they administered played probably an inferior rôle in the régime, though in popular belief they were assigned an important position. Their analysis (Ruston) showed them to contain the ingredients of Boerhaave's antidote (calomel and aethiops mineralis) and of the popular preventive pills of Schulz and others (colocynth, aloes, cloves, etc.).

Of greater importance in Daniel Sutton's régime were probably the attempts at attenuation of the virus itself and, in this regard, he probably learned from others, from Kirkpatrick and especially from Gatti, although it cannot be doubted that he himself was a capable observer and experimenter.<sup>51</sup> Attenuation of the virus was to be obtained in various ways: first by passing it through several human subjects (Kirkpatrick's arm-to-arm method),<sup>52</sup> by inoculating very small quantities of the virus and particularly by choosing it at the proper moment of development (the crude, unripe stage). We find all these points already suggested in Kirkpatrick's Charleston essay and, in passing, we may mention that Beddoes had tried to attenuate the virus by dilution with water, Woensel by mixing calomel with it, Kirkpatrick proposing camphor and other "scents."<sup>53</sup>

These efforts were all in the right direction, only it

<sup>50</sup> Of Robert Sutton we hear already in 1753 as an inoculator in Suffolk, where he experiments on himself and soon starts the business with three sons and a son-in-law, Dr. Hewit. Ten years afterwards his eldest son leaves him and begins on his own account at Ingatstone near Chelmsford (Essex), where he opens a hospital for inoculation and starts a flourishing enterprise with ramifications all over Great Britain and the Continent; his partner and assistants were Peale, Worlok, Sutherland and others.

<sup>51</sup> George Baker in 1766 tells us of Sutton's attempts at inoculating measles with the conjunctival fluid of patients.

<sup>52</sup> Thomas Frewen and others had already inoculated by this method in 1749 and abandoned Nettleton's deep incisions. Sutton seems to have avoided the virus from smallpox cases altogether.

<sup>53</sup> The admixture of musk to the virus practised by the Chinese may have had a similar motive.

appeared, particularly after Dimsdale<sup>44</sup> legitimized Sutton's method, that the attenuation was often carried so far that the result of the inoculation was sufficient to confer the desired immunity. Hence examples of relapses were cited and Bromfeild<sup>45</sup> had a right to fear that inoculation might become disgraced.

Sutton, Dimsdale and the others who adopted the "new method" did away effectually with the deep incisions, inaugurated by Nettleton and defended with so much tenacity. Slight punctures or scratches were now found to be amply sufficient and the disagreeable after treatment of the wounds was thus prevented. Tronchin introduced the virus into an artificial blister, a method followed extensively on the Continent and also intended to avoid the prolonged suppuration of the wound. This found little favor in England.

Thus the operation had reached a degree of simplicity, and lessened discomfort and danger, not thought possible before. Only the question of the protective value remained open. We remember that vaccination passed through similar phases and that relatively very late the necessity of re-vaccination became apparent. The test of repeated inoculations was resorted to quite frequently; we find reports of it all through the literature of those days. But experiments were also made to determine which part of the new régime and what kind of virus guaranteed the success of the operation. Watson,<sup>46</sup> who was physician at the Foundling Hospital where all children were inoculated, made some interesting experiments in 1767. Gatti was at that time in London and saw Watson often, which makes it very probable that he played some active part in them. Watson chose three parallel series of cases, 31 were inoculated with the virus from a smallpox case in the ichorous or watery state, 23 from another inoculated patient, but in the purulent state, and 20 others also from artificial smallpox with virus "in perfectly concocted state." This latter series was not "prepared" before inoculation, while the others went through the customary dietetic preparation (10 of the first series with calomel before and after inoculation). All of the patients were "out in the fields during the whole process." Watson gives a careful analysis of the results observed, some even in tabulated form, from which, as he puts it, every person is at liberty to make such deductions as he may think they will admit of. His personal conclusion is that the choice of the virus is not very material, that the ichor gives slightly better results, that the mercury has no specific effect and only acts favorably as a mild purgative. A well regulated vegetable diet before and during the whole process, the avoidance of heated rooms and heating liquors, he believes to be advantageous but not essential.

Re-inoculation experiments were undertaken by John Mudge<sup>47</sup> of Plymouth. Forty inoculations were made and seemed to demonstrate that "crude" matter taken from in-

oculation vesicles five days old does not convey immunity against a re-infection with natural or inoculated virus.

It is not evident that the results of these and other experiments exerted any revolutionizing influence on the method used earlier, but they must have helped towards perfecting it. The operation as then practised seems to have given satisfaction, for inoculations certainly became very popular in England, so much so that vaccination, in spite of the advantages which to us seem very clear, had first to subdue variolation before it could make any appreciable headway. It took exactly 44 years after Jenner's first vaccination, when, by act of Parliament, variolation was declared a felony.

Throughout this stage of evolution the Continent of Europe, in matters of variolation, is influenced by England. We see physicians arrive in London from various parts of Europe to study the method and on the other hand professional English inoculators travel all over the Continent to perform the operation, helping thereby its introduction.<sup>48</sup> Nowhere, however, did the practice reach the extent it had in England, although there is more noise about it and publications abound. This is a curious and notable fact, particularly when one considers that vaccination later was taken up in some continental countries more immediately and readily than in England. The first insistent plea for the introduction of variolation to the Continent was made by Voltaire from England where during his three years sojourn (after 1726) he had heard it discussed and had seen it practised in that country. That friend of John Locke's, Lord Peterborough, who, as we have seen, had brought Eller from Paris to London, took him also to his house. Voltaire made himself acquainted with everybody and everything with that eagerness so characteristic of him. Inoculation was on the wane just then, but its fundamental importance did not escape his keen mind. One of the many letters addressed to Theriot from England<sup>49</sup> is devoted to the subject of "l'insertion de la petite vérole." It is a most eloquent appeal. Motives common to all people, maternal tenderness and selfish interest,<sup>50</sup> he says, introduced inoculation to the Circassians. Then, by experience and observation of the disease and its peculiarities, this primitive people gradually evolves the idea of protective inoculation. How much more

<sup>44</sup> See Ebstein (*op. cit.*) about inoculations by George Motherby in Koenigsberg; Seitz about Baylies in Germany in Arch. d. Gesch. d. Med. II, 410; Chais (*op. cit.*) about Sutherland in Holland; Gardane (*op. cit.*) about Worlok and Seeby in France; Power (*op. cit.*) also in France.

<sup>45</sup> "Lettres philosophiques," at first called "Lettres sur les Anglais." Letter IX written in 1727 and also published in "Dictionnaire Philosophique," 1764.

<sup>46</sup> The Circassian and Georgian beauties were much in demand for the Turkish harems. Voltaire found the story of the Circassian origin of inoculation in de la Motraye's Voyages, etc., La Haye, 1727. Later travellers in the Caucasus found nowhere signs of inoculation being practised there. Creighton waxes indignant about this "myth constructed in cold blood." He thinks it is given "as a mere assertion in the manner of a *philosophe*" and therefore needs no refutation, whereupon he proceeds to give a long one. Evidently he is not Voltaire's friend. (Creighton, *op. cit.*, II, 473, note.)

<sup>47</sup> Thomas Dimsdale, 1712-1800.

<sup>48</sup> William Bromfeild, 1712-1792.

<sup>49</sup> William Watson, 1715-1787.

<sup>50</sup> For details the original ought to be consulted, also Creighton *op. cit.*, pp. 501 and 502.

can an advanced nation profit from this by perfecting the method! And Voltaire did not, after the manner of some *philosophes*, stop with this one dramatic appeal. We find that through his life he continues to exert his influence in favor of the method. Thus it was he who persuaded Catherine the Great, of Russia, to undergo the operation. Dimsdale was called (1768) and also inoculated the Grand Duke Paul and many nobles and others in St. Petersburg and Moscow. Returning he left in his wake an inoculation hospital here and indirectly one other in Irkutsk, Siberia! Indeed an evidence of Voltaire's far-reaching influence!

France was, however, not yet ready for inoculation. Only 20 years later did it receive a general consideration. The reason for this is not very easy to understand. De Mariveaux in a reply to that letter of Voltaire's explained it thus: *si nous n'inoculons pas en France comme en Angleterre, c'est parce que les Anglais se décident par le calcul, et nous par le sentiment*. Whatever the reasons may have been, the fact remains and we know only of isolated trials, principally in Paris. We must note here one serious effort which seems to have escaped most historians. Tenon, the excellent surgeon of the Salpêtrière, on his return from the campaign in Flanders (1745), quietly establishes an inoculation service in special premises annexed to the hospital. His interest in inoculation becomes evident only 10 years later when he inoculates the Comte de Châtelux, who in turn becomes an ardent champion of the cause. While Frenchmen on the whole were indifferent to the English example, the little republic of Geneva<sup>61</sup> had among its citizens men who evinced a distinct interest for everything English. Thus it may be explained how very early and determined efforts to introduce inoculation were made there. Already in 1748, Tronchin,<sup>62</sup> a Genevese settled for some years in Amsterdam, the favorite pupil of the old Boerhaave, had inoculated first his own son and then continued the practice among his patients. He introduced it also to Geneva where, on a visit in the summer of 1749, he inoculated a nephew, the son of the philosopher and magistrate Colandrin. Then the surgeon Guyot began to inoculate in September, 1750, and was soon followed by two physicians, Cramer and Joly. Trembley, the naturalist, another Genevese, had seen inoculations done in England and on the occasion of a visit to his home he suggested experiments in the hospital which were undertaken with encouraging results. In 1752 Guyot could report to Paris on his first 33 cases and others give accounts of even more, among them Buttini, who publishes an excellent essay. The practice is in full swing when Tronchin returns to Geneva (1754) and strangers flock into the town to be inoculated. In neighboring Lausanne Tissot,<sup>63</sup> who is already enjoying considerable fame as a

practitioner, has taken up inoculation and publishes, in 1754, a treatise which was to be one of the most read and quoted in all Europe. Tissot's warm friend in Berne, the great Haller, has his own daughter inoculated and becomes active in its recommendation. J. Bernoulli does the same in Bâle and gives an address on the subject at the University. Mieg in the same town, S. Schinz and I. K. Rahn in Zurich, report on their results, but nowhere in this country we now call Switzerland does inoculation flourish as in Geneva, and it is here that it is carried to its logical consequences on a smaller scale but to the same effect as in England.

Two other countries, parts of what is now Germany and Sweden, also obtained their inspirations in the matter of variolation from England. Hanover, belonging to the English Crown, saw the first inoculations, as already told. Haller was in Göttingen from 1736 to 1753. There had been a little stir about inoculation in Hanover nearly 12 years before he arrived, when Maitland came to operate on Prince Frederick and Wreden had published his *Vernünftige Gedanken*. But those events were forgotten and Haller had more pressing things to attend to during his stay. That he took an active interest in the subject becomes evident a few years after his return to Berne in 1753. Another great man, Haller's friend Werlhoff,<sup>64</sup> at Hanover, was present at the inoculation of three other English princes in 1754, and from then on continued to inoculate together with Berger and others. Zimmermann,<sup>65</sup> who in 1768 replaced Werlhoff on the recommendation of Tissot and Haller, kept up an interest in inoculation. Murray,<sup>66</sup> in touch with England (Pringle) and Sweden (Schulz), writes excellent pleas. At Göttingen several inaugural dissertations were devoted to the subject (Grimmann, Houth and others under Schröder) after Roederer,<sup>67</sup> Haller's successor, had shown the way. Wrisberg,<sup>68</sup> the eminent anatomist, devised a special instrument, by which the depth of the incision could be regulated and we see later his great pupil, Soemmerring, as one of the earliest and most earnest supporters of vaccination. I have already referred to the English itinerant inoculators. At all the many little courts of Germany we see them appearing. Baylies<sup>69</sup> seems to have been the most active. His advent marks the introduction of the Suttonian method in Germany (announced by Wichmann in Hanover). Between 1767 and 1775 we can follow his tracks everywhere. Frederick the Great who, already in 1755, had expressed his astonishment that so little was done in Prussia for a promising method, calls Baylies to Berlin in 1775. He is to teach 14 physicians from the provinces his method in the hospital. We have notes on this course made by one of the physicians and from them it does not appear that the teacher had anything new to teach. Bay-

<sup>61</sup> L. Gautier, *La Médecine à Genève*, 1906, p. 391. Gautier gives in this interesting medical history a full account of the progress of inoculation in Geneva.

<sup>62</sup> Theodore Tronchin, 1709-1781; see his biography by H. Tronchin, *Par*, 1906.

<sup>63</sup> S. A. A. D. Tissot, 1728-1797, one of the most famous practitioners and prolific writers of the 18th century.

<sup>64</sup> P. G. Werlhoff, 1699-1767.

<sup>65</sup> J. G. Zimmermann, 1728-1795.

<sup>66</sup> J. A. M. Murray, 1740-1797.

<sup>67</sup> J. G. Roederer, 1726-1763.

<sup>68</sup> H. A. Wrisberg, 1739-1808.

<sup>69</sup> Will. Baylies of Bath, 1724-1789.



lies had a dispute with Muzel, who, with the elder Meckel,<sup>60</sup> had inoculated some persons several years before with very poor results, and this was probably the cause of his rather sudden departure. Other eminent men, Pastor Süssmilch,<sup>71</sup> the founder of medical statistics, and Möhsen in Berlin, Ludwig in Leipzig,<sup>72</sup> Tralles<sup>73</sup> in Breslau, Hensler,<sup>74</sup> the medical historian, and Juncker<sup>75</sup> in a special *Archiv*, plead the cause of inoculation, but these are all isolated instances without any marked practical results, reflecting the political chaos which was only very gradually focussing itself into a national unit. Only during the last decade of the century do inoculations become more numerous (Juncker) but these are soon given up in favor of vaccination.

In Sweden and Denmark also we see influences carried directly from England and Hanover. Of the progress in Sweden, Murray gives an excellent account and from Denmark Callisen<sup>76</sup> is able to report numerous inoculations. In both countries it is introduced at about the same time (1754 to 1756); in Sweden by a personal plea of the King on the advice of the medical college and the support of eminent men, among whom must be named Rosén, Bergius and Schulz,<sup>77</sup> the latter publishing one of the best treatises on variolation. By the initiative of these men Sweden was receiving very early the benefits of an excellent medical and sanitary organization and inoculation benefits by it. Already in 1757 we see inoculation hospitals (Göteborg) founded and we learn from a letter of Baron Scheffer to la Condamine that systematic inoculations in the public schools of Stockholm are undertaken. In Copenhagen also an inoculation hospital is founded, after Baroness Bernsdorff, probably on the suggestion of Berger of Hanover, her physician, had submitted her children to the operation.

Tronchin's first inoculation did not immediately create a following in Holland. Only six years afterwards, in the year (1754), when he was leaving the country, we hear of the first inoculation performed by a Dutchman,<sup>78</sup> the excellent anatomist, Thomas Schwencke, at The Hague. In the same town inoculation finds an ardent defender in Pastor Chais and one of its most formidable opponents, Anton de Haën, who, however, is just leaving The Hague to go to Vienna. Thanks to the efforts of influential scientific men like Hovius and Camper<sup>79</sup> in Amsterdam, the interest in variolation is preserved and even carried to the Dutch Indies.<sup>80</sup>

The greatness of Dutch medicine slowly vanishes after the death of Boerhaave. Van Swieten<sup>81</sup> rapidly transplants the spirit of the Leyden school to Vienna. To count Van Swieten as one of the opponents to inoculation as is often done is not correct. We find him writing on July 23, 1755, to Dr. van Leempoel<sup>82</sup> from Vienna: "I am in favor of inoculation—and endeavor to introduce it here," and again in February, 1757, to de la Condamine that he is waiting for spring to begin experiments with it. It is not certain that these trials were then made, but we do know that later on experiments were certainly made with his consent and interested attention. The truth of the matter probably is that he kept above all parties. De Haën<sup>83</sup> on the contrary, soon after his arrival in Vienna, proclaimed his sweeping condemnation of inoculation. In 1759, in his "Questiones," he asks: "Is inoculation permissible before God? Will inoculated smallpox spare more people's lives than the natural disease? Is it really true that almost everyone must get the smallpox? Is it not doubtful whether inoculation, after conveying the disease or not, protects against a new attack?" All these questions de Haën answered emphatically in the negative, but with little solid substantiation. His ruthless attack on the promoters of variolation caused a literary stir. Tralles in Breslau, Tissot in Lausanne and de la Condamine in Paris answered by letters which really were treatises. De Haën thereupon pronounced a summary "refutation" of inoculation. His character is extremely difficult to understand, but as a teacher of great merit he undoubtedly helped Van Swieten in the reorganization of the medical school, thereby establishing its fame. Though ultraconservative, still interested in processes against witchcraft, which explains his interest in the moral side of inoculation, he was one of the first to utilize the thermometer clinically, while percussion, or Haller's teaching, did not interest him. His bark, however, must have been worse than his bite for he does not seem to stem the incoming tide of inoculation in Vienna. The Empress Maria Theresa, 50 years old, having recovered from smallpox, in 1767, on the recommendation of Pringle, calls Jan Ingen-Housz, a Dutch pupil of Dimsdale's to Vienna for the inoculation of two archdukes and one archduchess. The satisfactory result of the operation, after an extensive series of 200 test cases, opens the doors wide to the practice, which, particularly at the hands of Stoerck<sup>84</sup> and Locher, receives a thorough application and investigation. We have an excellent account of this period of inoculation in Vienna by Rechberger.

It remains now to review the subsequent fate of variolation in Paris, and in France and those countries more directly inspired from there. Paris was then, even more than it is now, the center of all activities in France and therefore it must appear strange that the most important local developments in regard to inoculation issued from two strangers, Tronchin and

<sup>60</sup> J. F. Meckel, 1714-1774.

<sup>71</sup> J. P. Süssmilch, 1707-1767.

<sup>72</sup> Chr. G. Ludwig, 1709-1773. Among his many writings is one of peculiar interest in regard to the study of medicine, *De medicinae studio non precipitando*, 1772.

<sup>73</sup> B. L. Tralles, 1708-1797.

<sup>74</sup> P. G. Hensler, 1733-1805.

<sup>75</sup> J. C. W. Juncker, 1761-1800.

<sup>76</sup> H. Callisen, 1740-1824.

<sup>77</sup> Nils Rosén (von Rosenstein), 1706-1773. P. J. Bergius, 1730-1790. Dav. Schulz (von Schulzenheim), 1732-1823.

<sup>78</sup> Van Leersum's account of inoculation in Holland in Janus, 1910, XV, 363.

<sup>79</sup> Jacob Hovius, 1710-1786; Petrus Camper, 1722-1789.

<sup>80</sup> van Hogendorp, v. d. Steeg, van Nielen (Batavia), *op. cit.*

<sup>81</sup> Gerard van Swieten, 1700-1772.

<sup>82</sup> Janus, 1910, XV, 368 (van Leersum).

<sup>83</sup> Anton de Haën, 1704-1776.

<sup>84</sup> Anton Frhr. von Stoerck, 1731-1803.

Gatti. When Gatti<sup>85</sup> appeared in Paris from his home in Pisa in 1760 he found, as he expressed it, "more brochures for and against inoculation than inoculations." This must have been very near the truth all through the whole period of variolation in France, for nowhere do we find anything approaching the number of inoculations reported in England, while we have to make our way through innumerable books, letters, pamphlets, fugitive leaves, etc., in order to get at the actual facts. Plentiful ideas are exposed with characteristic vivacity and sprightliness but reports of actual experiments are meager. When they do occur they almost always evince clear and penetrating observations. The war of pamphlets began in 1754, when de la Condamine<sup>86</sup> returned from a voyage of exploration in South America, whence he brought back the exact measurements of an equatorial degree, cinchona bark, rubber and, what interests us most, a deep conviction of the value of inoculation. A Carmelite missionary in Para had seen something in a European gazette about inoculation and, smallpox being in evidence, he at once inoculated his flock with excellent results. De la Condamine had seen him and his experiments and became convinced. He had no medical training, his leaning was towards mathematics and he had entered the Academy of Sciences, as he puts it, by the door of chemistry, the only one open. On April 24, 1754, a memorable day in the French annals of variolation, he addresses, for the first time, the Academy in favor of inoculation. His plea is based almost entirely on the English experiences as given in Kirkpatrick's "analysis" and some later publications including the reports from Geneva. As an embellishment are used the picturesque details of the "Greek method." It is one of those speeches the like of which we have often had occasion to hear in our own fight against the "white plague"; the danger is graphically described, the simplicity of the preventive means outlined, and the results to be achieved are mathematically fixed. "If inoculation had been introduced into France in 1723," concludes de la Condamine, "we would now have saved the lives of about one million people without counting their offspring." The effect of this address was that it stirred up great interest in inoculation. When one now reads the literature on inoculation which followed de la Condamine's *mémoire*, one gets the impression that, almost up to the advent of Dr. Guillotin's little instrument, nothing interested the French so much as how to save lives either with or without inoculation. That is probably what de Mariveaux meant by French *sentiment* as against English *calcul*!

Actual experiments, however, were very scarce. People in general, even those who took de la Condamine's views of the matter, seemed deadly afraid of the operation. We hear of the inoculation of some children on the advice of Turgot, a young lawyer and later a powerful minister. The Marquis de Châtelux was the first adult to go through the still dreaded

test.<sup>87</sup> An example from royalty was much needed. In almost every European court variolation had entered comparatively easily, probably because a preventive was most anxiously desired in those palaces crowded by a suite often numbering into the thousands and thus offering particular dangers. The Duke of Orleans, grandson of the Regent, who, by his death in 1723, had disappointed the early hopes of inoculators, was now determined to make the experiment in spite of small encouragement from Louis XV. A friend of Tronchin's, de Jancourt, probably persuaded him, and Sénac,<sup>88</sup> who only later became an opponent, approved of it. Tronchin arrives very quietly and the operation is performed towards the end of March on the two children, the Duke de Chartres and Mlle. de Montpensier, with the assistance of Hosty and Kirkpatrick. Everything goes well and Tronchin is the hero of the day. The psychology of this moment and the individuality of the principal actors are most interestingly analyzed in the biography of Tronchin<sup>89</sup> by one of his descendants, reviewed for American readers by Dr. F. C. Shattuck. Tronchin's stay in Paris was short, he departed in June, but it seems that during that time he performed a number of inoculations among the nobility. I am inclined to think that the number was very small and when the Duc de Luynes in his memoirs (March 28, 1756) says: "Tronchin pretends to have inoculated 20,000 persons," someone is grossly exaggerating. From Tronchin, who was not given to writing, we have no direct expression, but Roux, an eye-witness, gives (1765) a most interesting description of the whole method of treatment as carried out in the house Tronchin had hired for the purpose of receiving his patients for inoculation. They were "prepared" for it by a dietetic régime of one month. In the particular case cited by Roux 26 days were required from the time of inoculation to the final discharge, and 10 more for the healing of the wound. There were some rather alarming symptoms in this case and de l'Epine, referring to it later, thinks it was as bad as the real smallpox, but Tronchin, in a letter to Morel (1767), says that the patients treated by his method in Paris were less ill than those treated by the old method.<sup>90</sup> One really cannot wonder that people did not take to the old method and greeted the coming of Gatti a few years later (1760). He indeed brought simplification and perhaps went too far in the opposite direction, as some of his failures seem to indicate. Gatti hails from Pisa where he held the chair of medicine at the university. He was brought

<sup>85</sup> Buffon's words, when addressing de Châtelux at his reception to the French Academy in 1775, are: "Alone, without advice, in the flower of your youth, but decided by a maturity of reason, you went through the test then still dreaded."

<sup>86</sup> Jean-Baptiste Sénac, 1693-1770.

<sup>87</sup> H. Tronchin: Un médecin du XVIII<sup>e</sup> siècle, Theodore Tronchin (1709-1781), Paris, 1906, Plon 8°. See also F. C. Shattuck in Boston Med. and Surg. J., 1908, CLIX, 1-5. A less favorable judgment of Tronchin is to be found in a paper by A. Geyl, based on Dutch documents (Arch. f. Gesch. d. Med., 1908, 1, 81, et seq.).

<sup>88</sup> This case of Tronchin's as reported by Roux (1765) offers so good an illustration of the method as then practised, that an

<sup>85</sup> Angelo Gatti of Mugello (Tuscany) was professor of medicine in Pisa.

<sup>86</sup> De la Condamine, 1701-1774. He had already, once before, in 1732, attempted to interest the Academy in inoculation but failed.

to Paris by his friend Baron d'Holbach<sup>91</sup> and inoculated his children. Well introduced, he immediately found a great following. In 1763, 1764 and 1767 he publishes his ideas and the developments and results of his method in a direct and frank manner, which contrasted favorably with the mass of other writings. He co-operates with Roux, Antoine Petit, Bordeu<sup>92</sup> and others. His *réflexions* of 1764 particularly maintain a standpoint far in advance of his time. He sets out with a discussion of the etiology of smallpox. He objects to the lax conceptions then prevalent, expressed in vague terms of fermentation, ebullition, effervescence, humors, leaven, germ, etc. They mean nothing. Variola is always produced by the action of a foreign body introduced into the organism from the outside, by contagion or other communication. It is the constant and determinate effect of a specific "virus," which reproduces itself and multiplies. He insists especially on the specificity. Communication of the disease

extract may prove interesting: The patient is the son of d'Héricourt (*intendant de la marine*), 12 years old, delicate, anemic.

13. March 1756 régime begins, one-half of ordinary diet, chiefly farinaceous, some veal, mutton, chicken and vegetables. Every night tepid foot bath for one-half hour.
10. April. Roux moves with the young man, his pupil since 6 years, to Tronchin's house, where they sleep together in same alcove.
11. April. Surgeon Saint-Martin applies vesicant to insides of both legs.
12. April. *Inoculation*: Blisters are opened, threads with virus applied.
13. April. Removal of threads, bandage with digestive ointment, continued next day.
18. April. Around each wound red circle, beginning excavation.
20. April. Patient uneasy, headache, inguinal glands swell. Up to here from day of inoculation only vegetables, soup and barley water allowed.
21. April. Glands sensitive and painful, *fever sets in* 9 a. m. slight.
22. April. Fever higher, at 7 p. m. slight delirium, all night and next day, papules on chest.
23. April. Slight delirium and fever until 7 p. m. In morning slight epistaxis. During this febrile and eruptive period only barley water allowed.
24. April. No fever, eruption finished, slight nose-bleed.
25. April. Papules grow in size rapidly, some paler. Sixty-six on face and as many on body, distinct and with red circles.
27. April. Suppuration of pustules, wounds which were almost dry and covered by brown scab, begin to suppurate abundantly.
28. April. Some pustules begin to dry up. Saint-Martin opens some to take virus on threads.
4. May. (22d day after inoculation.) Exsiccation complete. Wounds discharge for 15 further days. During febrile period, diet same as before fever set in.
9. May. Slight "erysipelas" of face and around one leg, which continues for 3 to 4 days. "Patient subject to this." No fever. Roux calls this a benign case. He mentions by name seven other patients under the care of Dr. Tronchin at the same time.

<sup>91</sup> P.-H.-T. d'Holbach, 1723-1789, of German origin, but settled in Paris. He achieved some fame as a sceptic philosopher and entertained at his table all the *bels esprits* of the day. Galiani called him the *premier maître d'hôtel de la philosophie*.

<sup>92</sup> Théophile de Bordeu, 1722-1776.

takes place through contact, inhalation or ingestion. These were revolutionary views then, and to-day we do not know much more about variola. By inoculation, he goes on, the poison is conveyed by intelligence, in the natural disease by chance. A preparation of a subject for inoculation has sense only if it tends to improve his general health; debilitating measures like bleeding and purging, as practised by routine even on feeble individuals, have sometimes brought tears of pity and indignation to his eyes. As to the choice of the virus it is of lesser moment whether it is "crude" or "mature"; the important factor is that the individual from whom it is derived be in good general health and free from other contagious disease.<sup>93</sup> It is best to obtain the virus from another inoculation and he replies to the objection made, that the virus becomes hereby weakened: "There would be nothing left to desire in the art of inoculation, if we could arrive at attenuating the variolous virus, but I do not know any means by which this attenuation can be accomplished." The passage of the virus through several organisms may in time bring about a marked decrease of virulence and he adds prophetically: "Perhaps one day we may become indebted to inoculation for having brought about an attenuation of this poison among men." It is of no advantage to try and produce an abundant crop of pustules, *one* well developed pustule has as much protective value as a thousand. In case of doubt re-inoculation ought to be resorted to. With great vehemence Gatti turns against the unscrupulous practitioners, who, for selfish reasons, surround the method with all sorts of complicated details; he proclaims it a very simple operation and its chief principles are a thorough knowledge of the patient's condition and the art not to do harm, *partie la plus fine et la plus importante de la médecine*. He believes also that women could be instructed to the best advantage in the practice of inoculation. Gatti is absolutely convinced of the protective power of inoculated smallpox. He even substantiates this belief later by offering a considerable money prize for any authenticated case of re-infection after inoculation. Such cases, he thinks, can only happen when the eruption after inoculation is not one of true smallpox but is mistaken for it (he alludes here to chickenpox). He admits to have been deceived himself. The celebrated case of the Duchesse de Boufflers, illustrating such an instance, hurt Gatti's cause more than any other.<sup>94</sup>

After a careful consideration of Gatti's work and its proper

<sup>93</sup> Gatti admits that other diseases than variola can be conveyed by inoculation; it has happened to him with scarlatina and measles. Consumption (*pulmonie*) he does not believe to be thus transferred.

<sup>94</sup> "Je suis persuadé qu'il serait utile de pouvoir affaiblir la matière variolique, qu'il ne resterait plus rien à désirer dans l'art d'inoculer, si on pouvait y parvenir, mais que je ne connais aucun moyen d'obtenir cet affaiblissement."

<sup>95</sup> In the *Gaz. litt.* de l'Europe, Tome VI, p. 377 (also *Gent. Magaz.* Nov., 1765) is given a statement of the case by the Duchesse de Boufflers herself. It is widely discussed in France by de l'Epine, Ant. Petit and de Baux during the deliberations of the Faculty of Medicine. The best English account, with Gatti's explanations, is to be found in Langton, *op. cit.*, pp. 13-25. (Creighton gives an abstract in his book, II, 495.)



position in historical sequence, one is forced to the conclusion that the reformation which took place in the practice of inoculation during the sixties issued from him and that the success of Daniel Sutton and his followers is based on the methods advocated by Gatti. On the other hand it is evident that Gatti later on adopted some of the features of the Suttonian régime, notably the cold water applications and the open-air life. His adoption of the use of cold water is no blind imitation; it was based on the observation that whenever the fever, which usually follows the local eruption after three days, is delayed, the symptoms of the disease are lighter. By cold water applications he was able to delay the fever until the sixth day. But he makes no sweeping conclusions, he insists on further experiments and particularly on watching the relation of the local and general reaction.

The serious objection against inoculation, that of increasing the spread of the disease, Gatti frankly admits, but he believes that, since each infective focus is known, proper isolation could obviate any real danger. He seems, however, not to have been able to control all of his patients. That some of them had been seen to mix unhindered with others in public places was one of the chief causes of government interference. In a decree of Parliament, dated June 8, the General of Police alludes to the "murmurs of the Public" at the indiscretion of certain partisans of the method, which have "reached our ears." The "general cry" raised against the inoculators makes necessary an investigation by the enlightened magistrates. The *avocat du Roi*, Omer Joly de Fleury, then further enlarges on these reasons and concludes his address to the magistrates: "The fact of inoculation which now must fix your attention, presents itself naturally from two points of view, first as regards the principles of religion, secondly as regards the advantages humanity may derive therefrom." Experts in conscience and health will therefore have to be consulted. These of course are the Faculties of Theology and of Medicine respectively. The medical faculty is to give its advice first and then submit it to the theologians. The question of a continuation of a provisional tolerance to further "free literary discussion and various experiments" is set aside and it is decided to substitute for it a provisional prohibition against inoculating within the precincts of cities and suburbs until the named faculties have been able to recommend the permission, or prohibition, or tolerance of the practice.

From now on all inoculations have to be done outside the *barrières* and we see many go there, for the legally imposed limit of six weeks, to submit to inoculation. We know of numerous inoculations being performed under these restrictions by Gatti, Petit, Roux and others. Tronchin also sets up an establishment there in 1766 and Worlock,<sup>6</sup> the father-in-law of Sutton, and an assistant do the same.

Meanwhile the Faculty of Medicine goes to work on its report. A commission of twelve members is appointed and the procedure of investigation is outlined. This same faculty

which long ago had approved, then condemned antimony, and rejected the discovery of the circulation, proposes to decide this question again on similar evidence. Not the slightest effort is made to adduce further experiments, only the literature is to be studied and the opinions which inoculators outside of Paris are asked to express. Regular meetings are held by the commission, partly in camera, partly before the assembled faculty, and tumultuous scenes occur in which parliamentary methods are forgotten and personal encounters are threatened. The commissioners soon found they could not agree and decided to present two reports instead of one. Two groups of six each were formed, one, of those in favor, led by Petit, the other, of those against inoculation, headed by de l'Épine.<sup>7</sup> The former represented the younger, more progressive, the latter the older, conservative elements. Only 15 months after the parliamentary decree could the reports be presented before the assembled faculty for the first reading and, after acceptance, be put into the printer's hands. The publication, however, was delayed until 1766 and supplements were added as late as 1767. The report of de l'Épine would do honor to any prosecuting attorney; as such it is a very clever presentation of the case against inoculation. It occupies 125 quarto pages, mostly filled by the bibliographic reviews of the literature in fine print.<sup>8</sup> The main points are that smallpox is not so dangerous a disease as is usually asserted. De Haën had treated 120 cases with only five deaths, which may be explained as due to other causes. Bad treatment is at the bottom of most deaths. Furthermore many people never get smallpox and a fatal inoculation might strike just those. One such case is enough to condemn inoculation. Much is made of one of Gatti's failures and of the Boston reports (Delahonde) of an increase of smallpox following inoculation. In conclusion an attempt is made to show that the provisional prohibition has had already a favorable influence on the general health in Paris and "one begins to breathe again. The epidemic, no longer nourished and perpetuated by this unfortunate practice, has lost much of its force and is notably diminished."<sup>9</sup>

De l'Épine in his closing remarks suggests that the method

<sup>7</sup> The other commissioners in favor of inoculation with Antoine Petit were E. L. Geoffroy, A. C. Lorry, Maloët, Thiery and Cochu, while the opponents under G. J. de l'Épine's lead were, Jean Astruc, M. P. Bouvart, Th. Baron, J. Verdelhan de Miles and H. J. Moequart.

<sup>8</sup> Three separate sessions of the faculty were needed for the reading of this part of the report, viz., Oct. 20, 22 and 24, 1764.

<sup>9</sup> The summary of the conclusions is given in "nine incontestable truths" as follows:

1. Incertitude of conveying smallpox by inoculation, even if repeated.
2. Unsuccessful inoculation does not protect in future.
3. If successful there is no guarantee that attack will be benign.
4. If death is not issue, frequent disturbances may follow.
5. Same risks as in natural smallpox, disfiguration, etc.
6. Escape from death after inoculation insures no protection against other often more dangerous attacks.
7. Other diseases may be conveyed through inoculation.
8. Inoculated smallpox is sometimes fatal.
9. It can infect others and thus endanger society.

is perhaps not sufficiently perfected and hopes that the English may succeed, then "we shall thank heaven for such a precious discovery and we shall render them due homage for the enlightenment which they have procured for us at their risk. It would be unjust for us to envy them the very legitimate advantage of enjoying the first fruits, reaped under such perilous circumstances." The inevitable advice of these six commissioners is neither to permit nor to tolerate inoculation.

Of the signers of this verdict Astruc<sup>100</sup> was undoubtedly the most famous and influential. Eighty years old and only two years before his death, it cannot be presumed, however, that he took a very active part in the composition of this report. Bouvart,<sup>101</sup> another member, we can safely make responsible for several of the more extreme attacks against the inoculators. He was a violent antagonist of Tronchin's, whose book on the colic of Poitou he had tried to drown under a flood of ridicule and unjust criticism, and with Petit, the editor of the other report, he had had a quarrel about the very important question of belated childbirth.<sup>102</sup>

The report of the other party, edited by Petit,<sup>103</sup> is not nearly as carefully prepared as the de l'Épine document. One feels that it is written by a busy practitioner who has little time and inclination to enter into all the subtleties introduced. He judges from what he has seen, simply brushing aside the objections. It is not nearly as convincing for the casual reader as the other, in which almost all the reports of inoculators are dexterously turned against themselves, thus exhibiting a formidable array of damaging testimony. Petit did not follow such tactics in his first report, but, seeing that he had failed to make an impression, comes out in 1766 with a second report in which he shows the malice of de l'Épine's method. He points out the "multiple errors and mistakes of all sorts" and these become evident enough when one compares them with the sources.

This second report is signed by only three of the commissioners besides Petit, viz., Geoffroy, Lorry and Maloët,<sup>104</sup> the other two are absent and the Doyen Belleteste and the censor Le Thieulier therefore sign in their stead.

The endless discussions<sup>105</sup> about the merits of inoculation during these several years must have exhausted the interest in the subject and indeed, after the assembled faculty had expressed itself in favor of the tolerance of inoculation under certain restrictions by 52 votes against 26, we hear little more on the subject. Petit, in a later letter to the Doyen of the Faculty, thinks that, up to the end of 1766, probably 15,000 inoculations had been performed in France, which seems little

against the 200,000 reported from England. Although the acuteness of popular interest<sup>106</sup> had subsided, we have good reason to assume that inoculation was continued in Paris and the provinces on a much larger scale. We have, however, no evidence that anything was done, as in England, to further study and develop the method.<sup>107</sup> We should naturally expect to hear of Gatti's further work, but there is very little to be found about him. In 1769 he receives permission to inoculate in the military college, but of his results and the details of his work I have been unable to detect traces. Louis XV dies of smallpox in 1774 and this event decides his grandson and successor, Louis XVI, to submit himself as well as his family to inoculation. Neither with Louis XV's illness nor with this inoculation do we find Gatti's name connected, although he was physician extraordinary to the King.<sup>108</sup> Gatti's appearance and activity marks the greatest advance in variolation which was reached in France and, as a matter of fact, anywhere. His ideas and methods were those of the best scientists at the end of the 18th century and it is indeed remarkable how little his work is remembered.<sup>109</sup>

In England, and to some extent also on the Continent, after the technical principles of variolation became fairly well understood, we can see developing round it a social movement for the eradication of smallpox very similar to the tuberculosis crusade of our days. I have already alluded to the hygienic features in the regimen; they were enlarged upon and generalized for a wider application. Segregation of the infected cases was insisted upon more strongly than before. Early inoculation of infants was advocated by Maty and more emphatically by Lettsom. The demands for inoculation dispensaries became very loud and several were established (John Clark at Newcastle, Haygarth at Chester, etc.). The number of inoculations practised was exceedingly great. It went to many thousands per year. We have, of course, no accurate reports about it. But already in 1766 (Houlton) we hear that

<sup>100</sup> John Wilkes during his exile in Paris seems to have become interested in inoculation to the extent of writing a farce about it (*op. cit.*).

<sup>107</sup> The principal clinical reports of this time, besides the ones already cited, are those of Robert, Rast, Grassot, Rasoux, Dezoteux, Le Camus, Gardane, Gandoger de Foigny, Mangin, Vernage (*op. cit.*). Théophile de Bordeu, the founder of the theory of "vitalism" publishes (*op. cit.*), in defence of inoculation, a long historical treatise, in which he analyses what attitude the founders of all the medical doctrines since Hippocrates might have assumed in regard to inoculation.

<sup>108</sup> Report by de Lassone (*op. cit.*).

<sup>109</sup> In his own country, Italy, he does not seem to have exerted any great influence in favor of variolation. The considerable development which it reached there was inspired chiefly from France, Switzerland and Austria. The personal initiative of the Marchese Bufalini in Rome in 1754, the opposition of the Papal physician, Zanettini, and of Dr. Roncalli Parolino, and Tronchin's inoculation of a Bourbon prince in Parma are the main events of the Italian history of variolation. The most active Italian inoculators were Peverini, Lunadei, Lavizzari, Caluri, Targione, Manetti, Berzi, Bicetti (*op. cit.*). In Spain there seems to have been only a literary reflex of the French efforts.

<sup>101</sup> Jean Astruc, 1684-1766.

<sup>102</sup> M.-P. Bouvart, 1717-1787.

<sup>103</sup> The contention was about the legitimacy of a child born after an 11½ months pregnancy and 10½ months after the death of the 76-year-old father.

<sup>104</sup> Antoine Petit. 1718-1794.

<sup>105</sup> Etienne-Louis Geoffroy, 1725-1810, for 40 years one of the most prominent Paris physicians; Anne-Charles Lorry 1726-1786, good observer and medical historian of merit; P. L. Maloët, 1730-1810, able practitioner.

<sup>106</sup> Dubourg, *op. cit.*

Robert Sutton had inoculated 2514 persons from 1757 to 1767 and Daniel 13,792 from 1764 to 1766 and his assistants 6000 more.<sup>110</sup> As late as 1821 to 1822 John Forbes tells us that a farmer, Pearce and son, of Busham (Sussex) associated with some surgeons inoculated 13,000 persons!

Jenner's (born in 1749) interest in the subject dates from this period. John Hunter had told him already not to speculate but to observe and prove. With his natural gifts, with the inspiration of that particular period and the opportunities of his home surroundings it was inevitable that he should make the greatest improvement in the method of inoculation.

In following variolation on its course through the civilized world of the 18th century and, in noting the successive steps of its evolution, it has been my aim rather to open avenues for future research than to give a complete and detailed account

<sup>110</sup> His income for 1764 is given as £2200 and for 1765 as £6300.

of the more important phases. Plentiful suggestions are to be found everywhere which lead one to infer that variolation, without the advent of vaccination, might have furnished the world with an equally safe and perhaps more efficient method of preventive immunization. We have every reason, however, to be satisfied with the results of vaccination. Thanks to it smallpox has been practically stricken off the list of the great medical problems. None the less it is time that the epoch which preceded vaccination should receive its proper place in the history of medicine, and that the names of Kirkpatrick, Gatti, Watson, Mudge and Dimsdale should be recalled with that of Edward Jenner.

A full bibliography on variolation (over 600 items) has been collected by the author and is arranged under the headings: 18th Century, Americana and modern literature. It will appear in the reprints which Dr. Kleb's will be pleased to send anybody who will write to him.

## LECTURES ON THE HERTER FOUNDATION.

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### LECTURE II.

#### TRYPANOSOMIASIS.

The term trypanosomiasis is applied to-day to a group of diseases affecting vertebrates and caused by parasitic protozoa belonging to the family Trypanosomidae. These parasites occur chiefly in the blood plasma and the typical form possesses an elongated body, an undulating membrane, a single nucleus, a blepharoplast, and a chromatic filament running along its length from near the blepharoplast, along the margin of the undulating membrane, to terminate freely at one end of the body. The latter has a somewhat spiral form, the protoplasm being alveolar and at times showing a granular structure. An axial filament has been described as occurring in some forms. One species, *Trypanosoma equiperdum*, occurs largely in the lymph, and another, *T. gambiense*, may invade the cerebrospinal fluid. They are actively motile organisms, multiplying usually by longitudinal or multiple division. Numerous species have been successfully cultivated in vitro in the presence of haemoglobin and by this means many trypanosomes have been discovered in animals in which these parasites occur in such scanty numbers that their presence cannot be detected microscopically. Thus a large percentage of birds and cattle in different parts of the world have been found to harbour trypanosomes in their blood.

It would appear from the evidence gathered of late years that the majority of these parasites are conveyed from host to host by blood-sucking ectoparasites, either arthropods or leeches, whereas in some cases there is clear proof (partly experimental) that infection may take place directly from vertebrate to vertebrate through the contact of abraded or even healthy mucous membranes and skin. Although much has been written regarding a supposed sexual phase in the

life-cycle of trypanosomes, we are still in the dark as to its occurrence, the little evidence there is points, however, to its possible occurrence in the invertebrate hosts which serve as vectors, so that, at any rate provisionally, these may be regarded as the definitive hosts of the parasite. Infection may be brought about under experimental conditions by the inoculation of blood containing trypanosomes, or by applying blood to abraded or intact mucous membranes and skin. In nature, the infection of dogs by feeding on animals dead of surra (due to *T. evansi*) has frequently been observed, and similar results have been obtained experimentally. Dourine in horses is commonly communicated in nature in the act of coitus, and Koch suspected that the trypanosome of sleeping sickness (*T. gambiense*) might be similarly communicable in man, a supposition which has since been strengthened by laboratory experience. In one instance there is evidence that non-biting insects, *Musca domestica*, may serve as vectors; I refer to the equine disease "murrina" at Panama, due to *T. hippicum*, which is not apparently transmitted unless the animals show wounds of the skin upon which flies may alight and thus convey the parasites directly from host to host. In this case, also it is possible that infection may take place by coitus.

Judging from earlier evidence which proved that different species of trypanosomes could be readily communicated from animal to animal by inoculation, in some cases by the transference of minute quantities of blood, it was generally supposed that the parasites, under natural conditions, were communicated by biting flies in a purely mechanical manner. Experimental evidence on this point appeared, moreover, to bear out this supposition, for in a number of instances trypanosomes were transmitted from diseased to healthy animals by removing a fly from an infected animal upon which it was feeding and, soon after, transferring it to a healthy animal



upon which it was allowed to complete its meal. For a long time the classical experiments of Bruce, in Zululand, were accepted as evidence of the mechanical transference of *T. brucei* by *Glossina morsitans* (Fig. 10), he having found that infected flies captured in nature did not infect healthy horses if the flies were prevented from feeding upon them for 24 hours or more after they had been captured. Although some authors, notably in India, still regard mechanical transference by biting flies (*Stomoxys*, *Tabanus*, *Culicidae*) as of importance in the spread of infection, the general trend of opinion to-day is to regard such transference as possible, but of slight significance, in the epidemiology of trypanosomiasis.

Owing to the widespread interest evoked by recent advances in tropical medicine, a large number of observers in all parts of the world have devoted much attention to the study of microscopic parasites occurring in the blood of vertebrates. The result has been that we now know of a vast number of hosts which harbour trypanosomes in their blood, and the literature relating to new species of these haematozoa has grown to be one of considerable magnitude. The general tendency has been to consider each species of animal as the



FIG. 10.—*Glossina morsitans* Westwood.

carrier of a species of trypanosome peculiar to itself, this being doubtless due in part to the supposedly specific character of the adaptation shown by the parasite to its host. For a long time, one of the best known trypanosomes, *T. lewisi*, was regarded as peculiar to rats, and it is only recently that it has been shown to be also capable of living parasitically in other rodents. We know now that certain species of trypanosomes possess a wide range of pathogenicity, such forms as *T. brucei*, *T. gambiense*, *T. evansi*, and others being pathogenic for many different species of mammals. In some cases, morphological characters sufficiently differentiate the species, but our confidence in some of these characters has been shaken since we know that a species of trypanosome may alter its appearance in changing its host. Whereas the immunity reactions have been used to differentiate species of trypanosomes, a means of distinguishing species to which no zoölogist will agree, we now know that this means of differentiation cannot be relied upon since the virulence (an obscure character) of the parasites can be considerably modified experimentally.

Of the discoveries which have been made of recent years with regard to trypanosomiasis, those which concern the mode of infection by blood-sucking ectoparasites unquestionably spring into prominence both because of their great scientific

interest and practical bearing upon preventive measures designed especially to protect man and the more valuable domesticated animals against trypanosome infections. Sleeping sickness and nagana in Africa are amongst the most deadly diseases known, and I shall commence by outlining what we know to-day regarding the way in which they are spread.

#### SLEEPING SICKNESS.

*Trypanosoma gambiense*, the cause of sleeping sickness in Uganda and the west coast of Africa, is conveyed by *Glossina palpalis*. It has been estimated that 0.03-0.34 per cent of wild *palpalis* in the endemic area in Uganda are infective. Infective flies have been captured on the shores of Lake Victoria Nyanza which have been uninhabited by man for three years and they have been found on islands from which the human population has been removed for 10 months. There is no evidence that *T. gambiense* is hereditarily transmitted to the offspring of an infected fly, and it cannot be assumed that *palpalis* in nature can live for any such period. We were, therefore, forced to conclude that animals inhabiting this region must be susceptible to infection and capable of harbouring the trypanosome. It is now definitely established that certain animals do serve as "reservoirs" whence the flies may derive the parasite in the absence of man. The latest reports prove that antelope (bush-buck, reed-buck and water-buck) may harbour the trypanosome in nature. Antelope kept under observation have been seen to recover from any clinical manifestations of the disease and to appear perfectly healthy for 12 to 22 months, but they continue to harbour *T. gambiense* during this period and possibly longer, and throughout this long interval of time they may, as has been experimentally shown, infect clean *palpalis* which have been raised in the laboratory. Although there is evidence that with time the antelope's blood grows less virulent, as tested by inoculation into susceptible animals, and that antelope acquire a form of immunity, they harbour virulent *gambiense* for a sufficient length of time to maintain the parasite in nature in the absence of man. As in other diseases, so with trypanosomiasis, it is the chronic cases which serve as "reservoirs" for lengthy periods, and are most dangerous in relation to the spread and persistence of the disease in the region affected. The relation of game animals in respect to sleeping sickness in man is, therefore, similar to that of game in relation to nagana in domesticated animals; in both cases game may serve as a reservoir whence the *Glossinas* draw their infection. The wide range of pathogenicity possessed by *T. gambiense* renders it certain that it must, in nature, find reservoirs in other animals than antelope. In fact, the trypanosome has been recovered from cattle, monkeys (*Cercopithecus*, twice) and dogs under natural conditions. A large series of inoculations has been proved to be susceptible to infection by inoculation with *T. gambiense* of human origin. Without, perhaps, giving an exhaustive list, I would mention that, in addition to the animals already noted, the chimpanzee, macacus, lemur, cat, pig, goat, sheep, hedgehog, mouse, rat, guinea-pig, rabbit, horse and donkey have been found susceptible to infection with *T. gambiense*.

On the other hand, birds, reptiles and amphibia appear to be immune. The parasite has been conveyed experimentally to susceptible animals either by flies captured in a wild state or by clean flies purposely infected in the laboratory. Monkeys, sheep, goats and the duiker-bok have been successfully infected in this manner.

Experiments carried out with *G. palpalis* in captivity have shown that but a limited number—about 5 to 6 per cent—become infective after feeding upon blood containing *T. gambiense*.<sup>5</sup> In such flies a certain number of trypanosomes always degenerate and die but others soon begin to multiply rapidly throughout the gut, and this multiplication has been seen to continue within the fly's gut up to the 95th day, being maintained by repeatedly feeding the fly upon clean blood. The trypanosomes disappear from the fly's proboscis very soon after the insect has partaken of infected blood. The parasites occur in a variety of forms within the gut, they have not been found in the coelomic cavity, and it is only after a period of 25-28 days following the infective meal that they appear in the salivary glands of the insect. During the few hours immediately following an infective meal, the fly may transmit the trypanosome, this being doubtless due to parasites ejected from the proboscis before it has become cleaned. Then follows a period of 25-28 days during which the fly is incapable of producing infection. It is only when the parasites appear in the salivary glands that the insect becomes infective. The parasites in these glands resemble *T. gambiense* as seen in mammalian blood and they persist in the glands as long as the fly lives. Experiments made by inoculating the contents of flies into susceptible animals at various periods after an infective meal have given concordant results with those just mentioned. When the gut contents of a fly are injected into an animal within two days after it has been fed on trypanosome-containing blood, the animal becomes infected; from the third day onwards the results of similar inoculations are negative until about the 25th day, when injections of either the gut contents or salivary gland emulsion produce infection and these organs continue to be infective as long as the fly lives in captivity, i. e., up to the 98th day or longer.<sup>6</sup> *Trypanosoma rhodesiense*, now recognized as distinct from *T. gambiense*, is more closely allied to *T. brucei* than to *T. gambiense*. It is conveyed by *G. morsitans* and occurs in Northeastern Rhodesia and Nyasaland in cases of sleeping sickness in man. Apart from morphological differences, it has been found to be more virulent than *T. gambiense* and to occur more plentifully in the blood of man and animals infected with the

parasite. The high degree of virulence possessed by *T. rhodesiense* suggests that it is a new variety or species. Water-buck, hartebeest, mpala, wart-hog and native dog have been found to serve as reservoirs in the sense previously described. Flies captured in a wild state or raised clean and then infected in the laboratory have been shown to transmit the trypanosome. The fly becomes infective in 11-15 days (Kinghorn and Yorke, 1912, in North Rhodesia) to 35 days (Taute, 1911, at Tanganyika) and, coincidentally with its becoming infective, the flagellates appear in the fly's salivary glands. Only about 5 per cent of captive flies fed upon trypanosomatous blood become infective, but, as in the case of *T. gambiense* and *G. palpalis*, the fly, once infected, remains infective as long as it lives and it does not "clean itself" of parasites after repeated feedings on trypanosome-free blood.

#### NAGANA.

*Trypanosoma brucei* is conveyed by *G. morsitans* and *G. palpalis*. The well-known disease, nagana, to which this trypanosome gives rise, has been repeatedly transmitted by means of *G. morsitans* captured in a wild state in Africa. The parasite possesses a wide range of pathogenicity and can be transmitted for an indefinite period from animal to animal by inoculation of blood. We still maintain a strain of *T. brucei* in Cambridge which came from Zululand 15 years ago in a dog suffering from nagana, and it has been maintained by passage from animal to animal apparently with undiminished virulence. The greatest sufferers from nagana are apparently horses and dogs, man being unaffected. Once infective, *G. morsitans* remains infective doubtless as long as it lives. Tested under experimental conditions, this fly has proved infective 88 days after first imbibing the trypanosome. Through experiments with flies bred in captivity and consequently "clean" to start with, it has been shown that *G. palpalis* may also transmit *T. brucei*. As in *T. gambiense* and *T. rhodesiense*, it has been found that this fly does not become infective until about the 18th day and remains infective up to the 66th day and no doubt considerably longer.

#### SOME OTHER GLOSSINA-TRANSMITTED TRYPANOSOME INFECTIONS.

*Trypanosoma dimorphon* and *T. pecaui* also appear in the salivary glands when the flies become infective. These trypanosomes are transmitted by *G. tachinoides* and *G. longipalpis*; *T. dimorphon* may also be conveyed by *G. morsitans*.

*T. cazalboui*<sup>7</sup> is transmitted by several species of *Glossina* (*morsitans*, *palpalis*, *longipalpis* and *tachinoides*). When laboratory-bred flies are allowed to feed upon blood containing this trypanosome, 20-70 per cent of them become infected. *Glossina palpalis* becomes infective after 6-7 days<sup>8</sup> or after 17 days,<sup>9</sup> *morsitans* on the 9th day<sup>8</sup> or on the 21st-30th day.<sup>9</sup> After the fly feeds the parasites assume a crithidia-like form

<sup>5</sup> It is worthy of note in this connection that Ross and Milne have shown that *T. rhodesiense* exhibits periodicity in respect to its numbers in the blood. Miss Muriel Robertson has just reported what appear to be negative periods in monkeys suffering from trypanosomiasis. Although trypanosomes can be found in their circulation, the flagellates do not appear to have reached a stage in their development when they are capable of infecting *Glossina*. She reports, moreover, that a greater proportion (up to 21%) of *G. palpalis* become infected if the flies are starved for several days after imbibing trypanosomatous blood.

<sup>6</sup> A *Glossina palpalis* ♀ has been observed to live 227 days in captivity. These flies live on an average 4½ months in captivity.

<sup>7</sup> *T. vivax* is regarded as identical with *T. cazalboui*.

<sup>8</sup> According to French observers.

<sup>9</sup> According to British observers working in a different locality with "*T. vivax*."

(48 hours) and remain attached by the flagellar end to the labrum or hypopharynx; the infective forms, resembling trypanosomes, remain confined to the region of the fly's proboscis. Infection has been produced by inoculation of animals with the probosces of infected flies. The flies presumably remain infective for life, *palpalis* conveying the trypanosome to susceptible animals 75 days after having infected itself.

In all of the species of trypanosomes which have been enumerated (*gambiense*, *rhodensiense*, *brucei*, *dimorphon*, *pecaudi* and *cazalboui*) we have no evidence that the parasites are transmitted to the offspring of the flies which serve as vectors. In all cases the trypanosomes may occasionally be transmitted mechanically by the fly for a brief period after it has imbibed infective blood, and this is followed by a more or less lengthy period during which the fly is uninfected. Then, coincident with the appearance of parasites resembling the blood forms of the trypanosomes in the salivary glands or proboscis (*T. cazalboui*), the flies become infective and remain infective indefinitely. There is evidence that certain of these trypanosomes favour definite species of *Glossina* as hosts; if it were not so the flagellates would be even more widely distributed geographically than they are at present.



FIG. 11.—*Conorhinus megistus* ♀ after chagas.

#### CHAGAS' DISEASE.

*Schizotrypanum cruzi* Chagas, 1909, the cause of trypanosomiasis in Brazil is transmitted by a reduviid bug, *Conorhinus megistus* (Fig. 11). This vector occurs all over Brazil in badly kept clay and wooden houses and is a night feeder, the adult insect being able to fly. The bug moults five times before attaining sexual maturity in about 324 days. The bug becomes infective eight days after feeding upon infected blood and remains infective over a year. A female may live over 57 days without food.

The parasites, which are numerous in the blood in acute cases, multiply in the midgut of the bug. They are at first rounded, then crithidia-like, they then assume the trypanosome form in which they occur in the gut and salivary glands of the bug. Infection occurs through the infected saliva of the bug introduced in the act of biting, but the bug's excreta are also infective when fresh. I may add that Brumpt has recently observed the development of *T. cruzi* in *Cimex lectularius* and *C. boueti*.

The disease is communicable to dogs, cats, rabbits, guinea-

pigs, rats, mice, and monkeys (*Cercopithecus ruber*, *Hapale* and the Sajou). It is peculiar compared to other forms of trypanosomiasis, the thyroid gland being at times much enlarged (goitre-like). In some chronic cases there occur motor and cardiac disturbances, convulsions, infantilism and idiocy, etc.

#### TRYPANOSOMA BOYLEI LAFONT 1912.

Another interesting parasite of a reduviid bug, *Conorhinus rubrofasciatus*, has been reported upon this year by Lafont. The insect, which attacks man in Mauritius and Réunion, has been found to harbour flagellates, the intestinal tract of 50-80 per cent of the bugs containing the parasites. Lafont infected rats and mice by intraperitoneal injection with the gut contents of the bugs. In rats the parasites remain confined to the peritoneal cavity whence they disappear in about 30 hours. In mice, on the other hand, the flagellates appear in the blood stream in from 5-7 hours after inoculation and persist there for 1-5 days, after which they disappear and the mice usually die. When mice harbouring the trypanosomes in their blood, were bitten by the bugs, the flagellates resumed the forms (leptomonas, crithidia and trypanosome) which they originally possessed prior to entering the body of the mouse.

#### THE RAT TRYPANOSOME (*T. lewisi*) AND ITS MODE OF TRANSMISSION.

Whereas in the *Glossina*-transmitted trypanosomes the parasites enter fresh hosts through the flies' probosces, we have another method of infection in the case of the rat trypanosome.

*Trypanosoma lewisi* is conveyed by several species of flea and by the rat louse, it is world-wide in its distribution and occurs in 25-100 per cent of *Mus decumanus* captured in a wild state. Rats may harbour the parasite in sufficient numbers in their blood to render them demonstrable microscopically for a period lasting from a week to seven months. The usual vectors are unquestionably the common rat-fleas (*Ceratophyllus fasciatus* and *Ctenophthalmus agyrtes*) although the parasite is transmissible by other species of flea (*Ctenocephalus canis* and *Ctenopsylla musculi*) as has been demonstrated experimentally. Rat-lice (*Haematopinus spinulosus*) may occasionally serve as vectors.

*Trypanosoma lewisi*, after being imbibed by the flea, multiplies rapidly, chiefly in the hindgut and rectum of the insect. The parasites assume a crithidia-like appearance and occur in large bunches attached by their flagellar ends to the epithelium, or they occur in cyst-like masses within degenerating epithelial cells. Subsequently, the parasites resemble the blood forms as seen in the rat. They may then be found in vast numbers crowding the hindgut and rectum of the flea. The latter becomes infective in 4-7 days and it may remain infective for 45 days or longer. The flea does not infect the rat through its proboscis, and the parasites are not found in the flea's salivary glands. Infection can take place in three ways: the flea harbouring the infective forms of the flagellates may be (a) crushed and devoured by the rat, (b) the rat may lick



its fur upon which an infected flea has just dejected, (c) the rat may lick and infect with flea dejecta the wound produced by the insect. Fleas in the act of feeding frequently eject excreta which may be loaded with the flagellates in the infective stage. We have conclusive experimental evidence to prove that infection may occur in these different ways. We have then, in the flea, an entirely different mode of trypanosome transmission as compared to what we have seen in *Glossina*.

#### LEECH-TRANSMITTED TRYPANOSOMES OF FISH, REPTILIA AND AMPHIBIA.

*Trypanosoma granulosum*, occurring in the eel, develops in a leech, *Hemiclepsis marginata*. The flagellates at first multiply actively in the leech's stomach and afterwards in the intestine, where crithidial forms occur. Finally, the flagellates reassume the trypanosome form and appear in the proboscis-sheath of the leech. The latter only becomes infective when the flagellates appear in this situation.

The *Trypanosomes of the gold-fish*, bream, perch and rudd



FIG. 12.—*Hemiclepsis marginata*, anterior portion of living leech, showing position of trypanosomes or trypanoplasms in the proboscis sheath. After Robertson.

all develop in *Hemiclepsis marginata* (Fig. 12). They multiply enormously in the crop, undergoing a great change in appearance, being tadpole-like in form and having a crithidia-like arrangement of the nuclei. After the eighth day, slender trypanosomes appear, and after the tenth day they gather progressively in the leech's proboscis-sheath, where they cease to divide. The leech's bite is now infective and the flagellates are cleaned out of the sheath during the process of biting. The times when the leech becomes infective depends entirely upon the rate of the leech's digestive processes, it may be delayed to the 35th day, or longer. The leech still continues to harbour the trypanosomes; others present in the gut succeed those that disappear from the proboscis after each feed.

This leech may produce a mixed infection in fish for it also transmits *Trypanoplasma cyprini* which occurs in gold-fish and tench. This parasite divides rapidly in the crop, slender forms appearing on the second day and advancing on the sixth day so as to accumulate in the leech's proboscis-sheath in vast numbers. The flagellates attach themselves in this situation by their flagella and tend to crowd forward as the leech's digestion approaches completion, with the result that the leech may completely clean itself of parasites at a

single feed. It is worthy of note that the trypanoplasma does not materially alter its morphology in the leech. (Robertson.)

Trypanoplasmas have also been transmitted by the leech, *Piscicola geometra*, and a number of trypanosomes occurring in fresh and salt water fish (*T. danielowskyi*, *T. soleae*, *T. rajae*, *T. cotli*) have been transmitted experimentally by different species of leeches (*Hemiclepsis*, *Pontobdella*, etc.).

*Trypanosoma inopinatum*, which occurs in the green frog, is similarly conveyed by a leech. In this case, according to Brumpt, the flagellates are transmitted hereditarily to young leeches, thus offering a marked exception to what takes place in all other trypanosomes whose vectors have been determined. The leech concerned is *Helobdella algira*, and by means of this vector the trypanosomes have been successfully conveyed to *Rana esculenta* in which the flagellate does not occur in nature.

Finally, I would mention *T. vittatae* which is parasitic in a tortoise (*Emyda vittatae*) in Ceylon. Thus flagellate is transmitted by a leech (*Glossosiphonia*) in which it appears to behave in a similar manner to the fish trypanosomes above enumerated.

The general trend of recent work has gone to prove that, in the majority of instances, the trypanosomes of vertebrates are transmitted by blood-sucking ectoparasites within which they undergo a cyclical development. Whereas in the case of the *Glossina* mechanical transmission may occur, it must play a subsidiary part. In *Glossina*, *Conorhinus* and leeches, infection occurs through the mouthparts of the vector; in most *Glossinas* the flagellates are expelled from the salivary glands. In but a single instance (*T. inopinatum*) has it been claimed that the offspring of the vector (a leech) becomes hereditarily infected, and the statement awaits confirmation. In the rat-trypanosome there occurs a contaminative infection through the dejecta of the fleas or lice which attack a fresh host. Fleas and lice do not become hereditarily infected with *T. lewisi*. In dourine (*T. equiperdum*) direct infection from host to host in the act of coitus appears to be the rule, whereas it may occur exceptionally in other trypanosome infections. We are still ignorant as to the usual mode of infection in many trypanosomiasis, including surra and mal de caderas. In both cases the parasites (*T. evansi* and *T. equinum*) possess a wide range of pathogenicity and may produce chronic cases, so that there is every reason to believe, in my opinion, that reservoirs may play an important part in maintaining these diseases in nature.

#### POWERS OF ADAPTATION SHOWN BY TRYPANOSOMES.

Investigations conducted during the last few years have shown that trypanosomes possess considerable power of adaptation to altered conditions in the host, such as may be brought about by the administration of drugs. Trypanosomes may acquire a great resistance to the effect of a drug. At times this acquired resistance is accompanied by changes in their morphology, at other times no such changes occur. In the case of *T. brucei*, which becomes resistant to pyronin and

oxazine preparations, the acquired drug-resistance is accompanied by the disappearance of the blepharoplast. If these drugs are administered to an animal harbouring the trypanosome in its blood it will be seen that 40-90 per cent of the trypanosomes no longer show blepharoplasts after the expiration of 24 hours from the time the drug was administered. In this respect the oxazine preparation is the more powerful drug. If such trypanosomes are now passed through a series of 10 rats, each rat being in turn treated with the drug, it will be seen that the trypanosomes acquire a great resistance to the drug and that, with time, they no longer show blepharoplasts. If the trypanosomes have been subjected to the continuous effect of the drug for longer periods the blepharoplasts will not be reacquired even when the trypanosomes are passed through a series of 130 untreated animals. The oxazine preparation acts directly upon the blepharoplast. In trypanosomes which have reacquired their blepharoplasts a change of constitution has been brought about, for when they are subjected to the effects of arsenicals or trypanosan they again lose their blepharoplasts, this being contrary to what is observed in the normal flagellates.

In other cases no appreciable alteration in morphology accompanies the acquisition of drug-resistance. *Trypanosoma brucei* has been rendered resistant to parafuchsin (Franke and Roehl) and to atoxyl (Browning). In the latter case, this trypanosome has been found to remain drug-resistant during its passage through 140 untreated animals, this representing many generations of trypanosomes. There are, however, limitations to this resistance. Thus, Mesnil and Brimont found that *T. evansi*, rendered resistant to atoxyl to such a degree that the strain still remained resistant after passing through 110 untreated mice, when transferred to another host, the rat, immediately became susceptible to the drug whilst the rat served as its host. When the flagellate had passed through a series of 10 rats it was found, however, to be still atoxyl-resistant when returned to the body of the mouse. Similarly, atoxyl-resistant *T. equiperdum*, rendered resistant in the body of the donkey, has been passed successively through rats, guinea-pigs, rabbits and rats during a period of seven months and been found atoxyl-resistant upon being returned to the animal, the donkey, in which it was originally rendered resistant. From this we may conclude that atoxyl combines with a blood constituent to act upon the trypanosomes. When the flagellates have acquired resistance to atoxyl+mouse blood, they are still susceptible to atoxyl+rat blood or other blood than that of the mouse.

Of considerable interest, moreover, are certain observations of Gonder's (1911) upon arsenophenyglycin-resistant *T. lewisi*, wherein it was found that the resistance was retained for upwards of three months in cultures, but lost after a sojourn in the rat louse by which, as we have seen, the parasite is transmitted. The drug resistance is lost by the flagellate after about 10-12 days in the louse, and this fact may be brought forward in support of the view that the louse is a definitive host of the trypanosome and that a sexual development of the parasite occurs in the louse—the sexual process,

at a stroke, eliminating acquired characters previously maintained for thousands of asexual generations during the passage by inoculation from rat to rat.

This observation has a practical bearing in respect to human trypanosomiasis where arsenic-resisting strains of *T. gambiense* would be assumed, under certain conditions, as likely to be transmitted by *Glossina*. It will doubtless be found in this case, as with *T. lewisi*, that the passage of the flagellate through its vector renders it again susceptible to the action of trypanocidal substances.

In the time at my disposal I have only been able to dwell upon certain aspects of the subject of trypanosomiasis, and to bring out some of the many interesting problems which are being gradually solved by many workers.

The preventive measures directed against sleeping sickness have been dictated by experience gathered from research into the etiology of the disease, and, as our knowledge advances, so will our measures for combating the scourge have to be modified.

The hope that the disease would be exterminated by resorting to the inspection and segregation of natives, to depopulation and the destruction of the habitats which are suitable breeding grounds of *Glossina palpalis* have been but partially realized. The prolonged period of incubation and chronicity of the disease, coupled with the fact that fatal relapses have been known to occur after the lapse of years in apparently recovered cases render the disease very difficult to combat. A measure of immunity appears to be acquired after recovery, judged from animal experiment. Although treatment has given results which are encouraging, we are still far from the goal we wish to attain. The question of reservoirs has grown to be one of the greatest practical importance and the cry for the destruction of the game animals which serve as such is growing louder. It is for this reason that game destruction is at present being carried out over limited areas to see if it exerts any beneficial effect, although it appears very doubtful that this measure will prove useful, since it will drive the game elsewhere and so scatter the reservoirs into other regions. It is, moreover, by no means certain that domesticated animals would not have to be likewise destroyed, for they, too, may act as reservoirs. In view of the wide range of pathogenicity possessed by *T. gambiense* there is always the possibility of animals serving as reservoirs which it will be practically impossible to exterminate. On the other hand, there is hope that by reducing the number of reservoirs and *Glossinas* that the chain of parasitism may be broken, as it may be in malaria by mosquito reduction. Judging from the observations on *Glossinas* captured in a wild state, but a very small number of these are infective; the percentage of such flies may be sufficiently reduced to greatly lessen the danger of infection through their agency. In the case of *G. palpalis*, which has a relatively stationary habitat in proximity to water, we have a comparatively easy problem to deal with as compared to *G. morsitans*. The latter fly, which conveys *T. rhodesiense*, is migratory, it ranges widely and it resists dry-

ness such as *G. palpalis* cannot withstand, and, therefore, to attack its habitats successfully is practically impossible. A measure of protection will no doubt be afforded by putting the land, in the vicinity of human habitations, under suitable cultivation. We know that the main roads of travel are the most dangerous and that the old native measure in respect to magana of avoiding the fly belts during the day is safely to be relied upon.

It is clear that the study of the biology of the carriers of trypanosomes has become one of great practical importance, and that we are gradually accumulating data upon which we can proceed in a rational manner to combat trypanosomiasis.

NOTE.—Those desiring to consult the literature of *trypanosomiasis* are referred to the *Sleeping Sickness Bulletin*. The lecturer has purposely refrained from giving references so as not to burden the text.

## THE CHILDREN'S HOSPITAL, THE MEDICAL SCHOOL AND THE PUBLIC.\*

By L. EMMETT HOLT, M.D., New York.

The opening of any new hospital is an event which it is fitting we should celebrate, and I deeply appreciate the honor of being invited to a personal participation in the opening of the Harriet Lane Home for Invalid Children. A new hospital for children in this city means much to the community and to the medical school. I congratulate the City of Baltimore and The Johns Hopkins Medical School upon this event, and upon the selection which has been made of the head of this new institution, one of whom I can speak from most intimate personal and professional relations which have extended over a period of more than twelve years. I congratulate Dr. Howland on the opportunities which this splendid new hospital offers for teaching, for research and for practical experience. This building completed, and now formally opened, is the realization of the idea of a hospital for children in Baltimore which began to take shape when Dr. Emerson made his instructive report to the university upon children's hospitals in this country and abroad. If events have moved slowly they have moved surely.

We have in this country been slow to appreciate the need of special hospitals for children. Just as the specialty of pediatrics has been gradually differentiated from obstetrics on the one hand and general medicine on the other, so the evolution of the special hospital has been a slow one. Homes for foundlings most of our large cities have provided for many years. These, though necessary, have been in no sense hospitals; and often lacking in proper medical control, by their excessive mortality they have served as an example of how little philanthropy without science can accomplish in saving infant life.

In maternity hospitals infants are tolerated as one of the unavoidable incidents of obstetric practice. But the provision for them, and the attention bestowed upon them, even in our best institutions, is something which shocks the pediatricist. Certainly they have as yet failed to appreciate the hospital requirements of young infants.

The need for special hospitals for contagious diseases is latterly becoming generally felt. Of the fifty cities in the United States with a population over 100,000, thirty-four

have already established hospitals for the reception of the common contagious diseases, scarlet fever, diphtheria, etc. All but ten of these have come into existence since 1900. They are most important but limited in their sphere of activity. They have not supplied the need of a place where the common diseases of infancy and childhood can be studied and treated.

The necessity for special hospitals entirely devoted to children is something which is even yet scarcely appreciated in the United States either by the medical schools or the public. Only twenty-two cities are now provided with special hospitals for children. Is there a need for such institutions? Since hospitals are for the care of the sick, one may well inquire, who are the sick? Vital statistics of New York City show that twenty years ago 41 per cent of the total deaths were in children under five years, and that now, in spite of the great reduction which has taken place, these still form 33 per cent of all deaths. In the United States Census for 1910, Baltimore ranks seventh among the cities having the highest infant mortality, being exceeded only by Fall River, Lowell, Richmond, Detroit, Pittsburgh and Scranton. New York, with all its overcrowding, ranks fifteenth. The mortality in Baltimore of children under five years is the ninth largest in the cities of the country having a population over 100,000. It is surely incumbent upon the public to see to it that the age which includes fully one-third of all deaths should have adequate hospital provision made for it, and, what is even more important, adequate facilities given to specialists for study and investigation, and at the same time afford to students, practitioners and nurses opportunities for instruction and experience.

It is often urged that wards for infants and children in general hospitals are to be preferred to separate hospitals for this group of patients. Such wards have, it is true, been a part of the organization of the larger hospitals of most of our cities for the past fifteen or twenty years. But how has this worked? In many institutions the beds have been largely or exclusively given over to the care of orthopedic or other surgical cases. Where medical beds existed they have usually been made a part of the general medical service of the hospital, and the attending physicians who served in rotation a few months at a time, as a rule, gave scant attention to the needs of the special service. Equally unsatisfactory has been the attention given by the resident medical staff, when each

\* Address delivered Nov. 20, 1912, at the opening of the Harriet Lane Home for Invalid Children, The Johns Hopkins University.



member was given in turn two or three months in charge of this ward that he might gain some experience with children. The practical result of such an organization and administration has been that the service, especially as regards the infants, went by default, and very little was accomplished in advancing the knowledge of the diseases of children. With respect to organization there has been in some places an improvement by the appointment of a special attending physician to these wards. This is a practice which should invariably be followed. Yet in spite of this change I have personally no hesitation in pronouncing in favor of the separate hospital. The children's service in the general hospitals is in nearly all cases too small to admit of a proper classification and separation of patients. The only important argument which I think can be advanced in favor of wards in general hospitals is that of economy. A large institution can certainly be operated at a lower *per capita* cost than a small one, and the children's hospital must not be too large. That such a service as usually operated affords a valuable experience to the resident medical staff is open to serious question.

The construction, the equipment, the organization, and the operation of a hospital for young children are quite different from those needed in hospitals for adults. These grow out of two great difficulties which attend the hospital care of these patients: the problem of nutrition and that of ward infections. These necessitate smaller wards, ampler provision for the separation of patients in doubtful diseases, and in diseases of feebler communicability than our ordinary contagious diseases. Not only must there be sufficient provision for fresh air and proper ventilation for acute infectious cases and pneumonia, we must have also wards in which a temperature much higher than the usual room temperature can be maintained for the congenitally feeble, the marantic and the premature infant. The nutrition of feeble infants is always difficult even in a state of comparative health; but with acute illness added, the difficulties are greatly increased. The feeding especially must be exact and requires special equipment and specially trained service. There are many other particulars in which the operation of an institution caring for the very young must be carried on in an entirely different manner from methods pursued in an adult hospital. It has been my observation and experience that boards of managers, hospital superintendents, and head nurses can rarely be made to appreciate them. Forming only one department of a large institution, and that usually a small part, it is seldom the case that anything like adequate attention from an administrative point of view is given to the wards for infants and young children.

In the past our hospitals have represented our philanthropy. The modern hospital, while not losing its philanthropic character, is to be classed among the institutions of higher education. The academic hospital in particular is to be so regarded. Properly equipped and administered, it is altogether the most productive of all the college laboratories. Proper teaching does not interfere with the best care of the sick, but rather should contribute to it. This is particularly true of little children, who have no prejudices to overcome, no modesty to be shocked, and no sensibilities to be

hurt; but since they cannot describe their pains or express in words their wants, they require the closest kind of individual study and observation. No better opportunity can be afforded for the training of the medical student than to place him in a hospital ward with sick infants and teach him how to observe them. One who would succeed in this specialty must not only know disease, he must learn to understand children.

The provision for the care of patients must be of the very best; while not extravagant the best possible hygienic conditions for the treatment of the sick must be furnished. While it is important to give our students the scientific point of view, we must, at the same time, equip them with the facts and the training which will enable them to do as well as possible the common everyday things which are needed in practice. It is altogether probable that fully four-fifths of your students will be practitioners of medicine, and that the other fifth will, as parents, be called upon to put to practical use the teaching of this department.

Research work, while of the utmost value to the hospital, is of little importance to the average student. Now and then a genius appears in our medical schools who should be encouraged to take up new problems. But there are few men who are not the better for having spent four years, as a preliminary training, upon the regular courses. Only in this way can they obtain the breadth of view which will enable them to connect their scientific work with the great practical problems of medicine to-day.

Provision for research in the special hospital should be ample, and this department should be generously supported, for here are opportunities found in no other institution. The close association of the scientific and the practical workers under one roof is of immense advantage to both. Research work should not be conducted along pathological or chemical lines only, but it should be clinical also. All these lines of investigation should be carried on simultaneously. The present disposition to undervalue the clinical side and put the emphasis upon the purely laboratory side of research is most unfortunate. Students and young assistants should not get the idea that the only scientific observations in medicine are those made on guinea pigs. There is urgent need at the present time not only for technical training in the use of the newer aids to diagnosis, but for the closest kind of clinical observation of disease, especially in young children. Nearly the whole fabric of infantile therapeutics must be constructed anew from the standpoint of recent advances in medical science.

I do not mean that patients in the hospital are to be used as subjects for experiment; that phrase is likely to be misunderstood. But what is new and promising must be thoroughly tested under conditions in which the most careful observations are possible; and these can only be obtained in a hospital. Proper clinical studies upon patients necessitate a liberal provision for a resident staff and assistants. Their work, however, can, as already suggested, be advantageously supplemented by the medical student. All these three lines of work, student instruction, research, and the care of patients can be

carried on at the same time and each activity, instead of embarrassing the others, can promote them and thus the best possible results in all be attained.

I have already suggested that hospital work among very young children is quite a different problem from the hospital care of adults. There are some features upon which I would like to dwell for a few minutes. The first is that of hospital mortality. Nothing is more disturbing to hospital managers, nor at times more discouraging to a medical staff than the death rate, especially among infants. While, in a broad sense, it is true that the value of the work is to be measured by the number whose lives are saved or whose health is restored, this must not be too narrowly construed. To compare the mortality figures of such a hospital with one admitting only adults is most unjust. The proper comparison is between young children treated in a hospital and those of the same class treated outside of it. We have seen that children under five years furnish a third of all the deaths. In different cities the mortality during the first year of life varies from 150 to 350 per 1000 of infants born. Infants are the first to feel the effects of an unfavorable environment, they are the most susceptible to disease and have the smallest resistance to it. Whether they are received into hospitals or not the mortality of infants is very high, unnecessarily high. In the City of Baltimore your infant mortality in 1910 was 383 per 100,000 of population.

It is to reduce this excessive death-rate to the minimum that the hospital for children must work. Obviously any such institution which does its duty to the community, and admits very sick infants, will have of necessity a high death rate. This can, of course, be reduced by the simple expedient of refusing admission to apparently hopeless cases. I have known institutions which resorted to this in order to make a good showing in annual reports. But it is a narrow and contemptible sort of philanthropy which would countenance such a practice. A hospital exists for the sick, and the sicker the patient the greater the reason why he should be received in a hospital which is presumably equipped with every facility for saving life. Nearly one-fifth of the deaths in the Babies' Hospital, in New York, are in patients who live less than twenty-four hours after admission. But if such children were not received, in many instances, they would have died in the mother's arms while walking the street. For a period of years in this institution, which receives only infants and children under three years, the average mortality has been about 30 per cent. Something like this is to be expected in every hospital which admits the same class of patients. But to hospital managers I would say, do not measure the usefulness of your institution to the community by the death rate, but regard this as an indication of the kind of patients admitted. Year by year as science advances, and your institution grows in efficiency, you will note with satisfaction a steady reduction in the death rate with the same class of patients.

Another feature of hospital work among very young children is the frequency of ward infections. Not only are measles, scarlet fever, whooping cough and diphtheria to be guarded against, but more difficult to combat because the means of

spreading is less obvious are infections due to the pneumococcus, streptococcus, gonococcus, and influenza bacillus. They are responsible for many more deaths than are the common contagious diseases. All of these necessitate the detention of patients in observation rooms before admission to the general ward; adequate space between cribs, or the erection of partial partitions between them to prevent bed to bed infection, hygienic sweeping and dusting; the most scrupulous cleanliness in wards to prevent aerial infection through dust; constant care regarding towels, bath tubs, wash clothes, napkins, thermometers, and in fact everything which comes in contact with the patient. All of these things and many more which time does not permit me even to enumerate, indicate that in a hospital ward for infants we must aim at conditions which at present, in most institutions, are realized only in the surgical operating room. The susceptibility of these patients to infection is certainly comparable to persons with open wounds. You are thinking, perhaps, that what I have said is impractical or impossible, and that it would not be worth while. So surgeons once thought of rigid asepsis. Hospital work for infants is admittedly difficult. Unless it can be well done it should not be attempted; but when it is properly done, the results will bear comparison with those obtained in any other department of medicine.

I have not time to dwell upon the necessity for the most ample provision for nurses, if such results as we have been contemplating are to be obtained. The needs of adult patients in this respect are no criterion. At least one nurse to three infants by day, and one to eight or nine at night are necessary even for patients not acutely ill.

The conditions under which only successful hospital work for young children can be carried on impose certain limitations with regard to the size of such an institution. I do not believe that the best work is possible in hospitals of this class with three or four hundred beds. Several small ones would accomplish much more. The one hundred beds provided in this institution I do not think should be increased. This will provide probably an average number of seventy-five patients, which will furnish ample material for the instruction of students, and are all that can advantageously be cared for by a single medical head. This ward service should be supplemented by an out-patient department which may be of indefinite size.

On the part of hospital trustees and managers there is often a disposition to consider the size of the work done as a measure of usefulness. But it is the quality of the work by which a hospital should be judged, not the quantity, for if the quality be poor, the larger it is the worse for the public and the profession. Numbers do not count in science so much as other considerations.

In New York, at least, the greatest embarrassment to the scientific study of disease in hospitals is the size of the service, and the demands made upon the medical and nursing staff for the routine care of the sick. The time needed for the thorough study of difficult and obscure cases is not to be found and progress in clinical medicine is therefore slow. I mention these points, not because they are new, for every hospital

physician fully appreciates their force, but in order that lay members of hospital boards may get the point of view that the chief function of a children's hospital is to determine, by careful observation in the diagnosis and treatment of the few, how the many must be treated. The best results are to be obtained by the intensive method of study, not the statistical method.

Some of the discouraging features of hospital work for children have been mentioned. There is another side of greatest encouragement. The great difficulties are to be found in the first year. After this age children are the most hopeful patients to deal with. Nowhere else does effort tell so effectively in results. With adults hospital work is, much of it at least, only patchwork, putting an old hulk into such repair that it may keep afloat and do duty a little longer. With children it is more like new construction, starting a new life straight, with all the satisfaction which this brings.

A special hospital like this can do much for the community besides caring for the sick poor. It sets a standard of medical practice for the profession of the city. It is an exponent of modern science in its particular field. Here should the best hygiene be illustrated, the best feeding be practiced, and the most intelligent care of the infant sick or well be exemplified. Such ideas spread gradually from those immediately connected with the hospital to the general public.

One of the most effective means of influencing the public is by nurses who have been educated in the institution. Not only should trained nurses be taught a knowledge of children and their diseases, but a school for training nursery maids in the care of healthy infants should be established as a constituent part of the hospital. The need of the public in this respect is so great that the opportunities which the hospital affords to give this instruction should be utilized. This is a by-product of hospital organization and operation that is of great importance, and will prove of advantage to an institution needing public support.

The educational value to the public of an up-to-date special hospital like this can hardly be exaggerated. It is destined to take its place among the great forces for social uplift in the department of child welfare. The City of Baltimore should have as much interest in its development and as much pride in its success as the medical school. The people of the community will need to be educated up to the advantages which the hospital offers over the home, especially the homes

of the poor, for very sick children. With many of this class a prejudice against the hospitals, born of ignorance, must be overcome before they will consent to entrust their children to its care. To gain confidence is a matter which takes time, but the establishing with parents and relatives the most friendly and sympathetic relations is something, the importance of which every one connected with the hospital as superintendent, doctor, nurse, or employee should appreciate. It has to do with the practical success of the institution in many ways. Upon no one thing does the accurate diagnosis of disease depend so much as upon autopsies. The facilities which the hospital affords for seeing autopsies constitute one of its greatest uses. I know of children's hospitals where these are permitted upon less than 10 per cent of the fatal cases. What a loss to science this represents. For the medical staff and students who have long watched an obscure condition go on to a fatal termination, not to have an opportunity to clear up the mystery is most discouraging. In another institution with which I am personally connected, consent for autopsy is obtained in 70 per cent of the cases; and this has been accomplished largely through the influences which I have just suggested.

The hospital occupies a place in modern civilization of steadily increasing influence and importance. On the one side it must be in close touch with teaching and medical research, and on the other with the needs of the public. The spirit of an institution is something different from its aims. It is the resultant of the attitude of mind, the breadth of outlook, and the personality of the three persons who determine the hospital's policy: The dominating spirit in the board of trustees, the superintendent, and the physician-in-chief. A hospital should be managed efficiently and scientifically, but more than this, it should be managed humanly, keeping in sympathetic relations with the class who form its patients. May we in this country, be delivered from the cold-blooded science which dominates so many of the hospitals abroad, where patients are regarded only as so much *material*. We must not forget in our hospitals, or in our medical teaching that the ultimate aim in all our work is to minister to the suffering and the unfortunate. We need to keep such ideals before the minds of the medical student quite as much as to arouse his enthusiasm for science, and to arm him with the skill and experience which will fit him to practice his profession.

## IN MEMORIAM.

DR. ROBERT FLETCHER.

Doctor Robert Fletcher, for thirty-five years the principal assistant librarian of the Library of the Surgeon General's Office, died in Washington, November 6, 1912, in the ninetieth year of his age. The end of such a long and useful life calls for more than passing notice, for to the great learning and accurate editorial work of Dr. Fletcher on the Index Catalogue

and Index Medicus the medical profession of America and Europe is deeply indebted.

Doctor Fletcher was born in Bristol, England, March 6, 1823, the son of an attorney and accountant of that city. He was educated at private schools in Bristol and read law with his father for two years before taking up the study of medicine at the Bristol Medical College and later at the London Hospital, of which he was the oldest living graduate. He became Licentiate of the Society of Apothecaries and member of the Royal College of Surgeons in 1844, married in 1843 Miss



Hannah Howe of Bristol, and came to the United States in 1817, making his home in Cincinnati.

At the outbreak of the Civil War Dr. Fletcher was commissioned as Surgeon in the 1st Ohio Infantry and was on active field service for two years. In 1863 he was made Surgeon U. S. Volunteers and assigned to the army of General George H. Thomas in the Nashville campaign. He was in charge of Hospital No. 7, Nashville, Tennessee, and subsequently medical purveyor at Nashville and Cincinnati where he wound up successfully the complicated affairs of a war-time purveying depot, receiving for "faithful and meritorious service during the War" the brevets of Lieutenant Colonel and Colonel. The War Department employed him in 1871 to assist in the preparation of the two valuable volumes of "Medical and Anthropological Statistics" of the Provost Marshal General's Bureau, derived from the examination for military service of over a million men. For this work Dr. Fletcher wrote the introductory treatise on anthropometry, about the only thing of interest to the general reader in this book, and which illustrates very well the extent of his information and his love for the historic and artistic aspects of medical science.

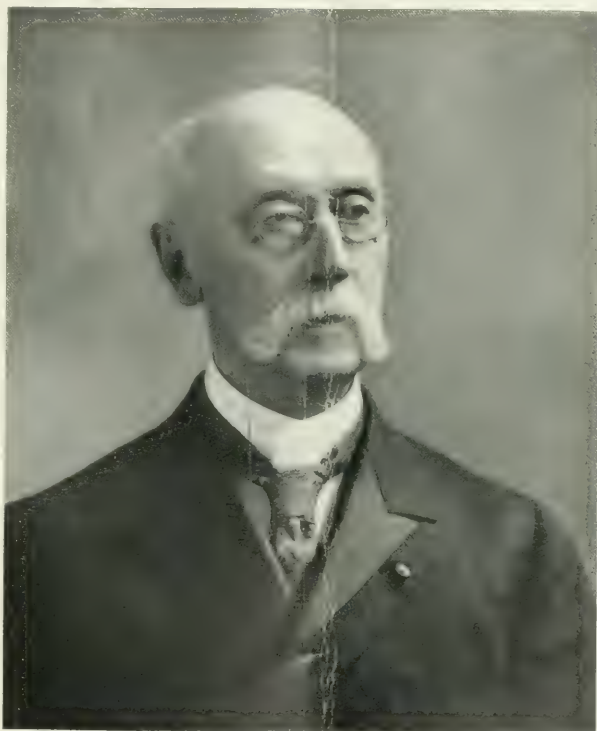
The library of the Surgeon General's Office, an absurdly small and insignificant collection of books in 1861, had increased during the war to about 1700 volumes. In 1865 Dr. John S. Billings, then Assistant Surgeon, U. S. Army, was put in charge and began to develop what is now perhaps the largest and best known medical library in the world, a monument to the energy and forethought of its founder. As the library rapidly increased in size and importance, Dr. Billings prepared the plan of the present Index Catalogue in which under a single alphabet and in dictionary order a combined index of authors and subjects appears. The "specimen fasciculus" of the proposed catalogue was printed in 1876 and submitted to libraries and bibliographers for comment and suggestions. Soon after its appearance the services of Dr. Fletcher were secured as principal assistant to Dr. Billings in the work of preparing and printing the Index Catalogue of which the first

volume was published in 1880. From that time to the past year (1912) a volume has appeared annually, and the first series A to Z having been completed in 1895, the second series now reaches the letter T. On these 33 massive quartos averaging nearly 900 pages to a volume and containing to date 327,000 author titles and 1,333,079 subject titles of books, pamphlets and original papers in periodicals, Dr. Fletcher labored to within a few weeks of his death, supervising, proof reading, and correcting with tireless patience and extraordinary accuracy. Much original work of a high order is

called for in the grouping and subdivision of the subject matter of the Index Catalogue, requiring a vast amount of information which must be kept abreast of the times by constant study. The almost revolutionary changes in medicine and surgery and the evolution of many specialties which characterized the last years of the nineteenth century and the beginning of the twentieth, found Dr. Fletcher already an old man, but to the last he constantly added to his great store of knowledge and his fine intellect as readily appreciated the latest medical paper of real value as the venerable volumes of the old masters of medicine in which his bibliophile's heart delighted.

The Index Medicus, a monthly publication based upon the card catalogue of the Library of the Surgeon General's Office, and which supplements the Index Catalogue by bringing to the public notice the current medical literature before it can be reached in alphabetical order, was begun in 1879 with Dr. Billings and Dr. Fletcher as co-editors and ran until 1899 when the publication ceased. It was revived in 1903 under the auspices of the Carnegie Institution with Dr. Fletcher as editor-in-chief until his resignation in the early part of 1912.

Away from his editorial work Dr. Fletcher found time for many social and literary interests. He was sometime president of the Anthropological, the Philosophical and the Literary Society of Washington and the president of the Cosmos Club. He lectured on medical jurisprudence at the Columbia University of Washington, 1884-1888, and at the Johns Hop-



ROBERT FLETCHER.

and physicians, 1897-1904. In spite of, or perhaps on account of, his professional life, he was led to pursue some of the same aims in medicine of special interest to him, and as a result he produced many original essays on anthropology, early jurisprudence and medical lore, as known to the old poets, dramatists and artists. In his writings, he is always master of his subject, clear and simple in style and with a certain quiet humor which is most attractive.

A complete list of his literary productions will soon appear in the *Index Medicus*, the last essay "On Some Diseases Bearing the Names of Saints" having been published after his death in the December number of the *Bristol Medico-Chirurgical Journal* preceded by a graceful "In Memoriam" by Sir William Osler, a friend of many years standing.

Doctor Fletcher was a handsome soldierly man, dignified and courtly in manner. He also possessed to the full the blessed sense of humor and was a philosopher who had learned to extract all that is best in life. Time dealt very gently with

him. Except for the feebleness of extreme old age his health was excellent and his mind remained unimpaired.

Dr. Fletcher's service to the profession was acknowledged by many honors, among which was a banquet given by leading physicians and scientists on January 11, 1906, with a loving cup and a commemorative album which was one of his most prized possessions. In 1910 he was awarded the gold medal of the Royal College of Surgeons, a rarely conferred distinction. He was an associate fellow of the College of Physicians of Philadelphia, honorary M. D. of Columbian University and a few weeks before his death received a degree in medicine from his first medical school in Bristol. He had many devoted friends, young men as well as old, who delighted in his company and enjoyed his conversation at his favorite club or in his charming private library where he lived alone with his books.

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## NOTES ON NEW BOOKS.

*Bacteria in Relation to Plant Diseases.* By ERWIN F. SMITH. In charge of the Laboratory of Plant Pathology, Bureau of Animal Industry, U. S. Department of Agriculture. (Published by the Carnegie Institution of Washington, 1913.)

The second volume of Dr. Erwin F. Smith's *Bacteria in Relation to Plant Diseases*, which bids fair to become the most exhaustive and authoritative work on the subject of plant bacteriology in the English language has recently appeared. The first volume was published in 1905. To understand the significance of these two volumes it is necessary to remember that it was the botanists of the old world who laid the foundations upon which the modern science of bacteriology was built up. The fundamental investigations of Ferdinand Cohn in the Botanical Institute of the University of Breslau paved the way for the epoch-making discoveries of Robert Koch in the domain of the bacteria pathogenic for animals and man. To the botanist of the decades from 1870 to 1890, however, bacteria were objects of study because of their biological or botanical characters. They formed an important part of those natural objects which came directly within the sphere of botanical investigation. The fact that bacteria themselves, classed among the lowest forms of plant life, could be the cause of important diseases of plants seems to have been recognized but slowly by the botanist. Indeed, as Dr. Smith points out in the historical introduction to Volume II, up to the year 1893 but a small number of plant pathologists were interested in trying to determine whether the bacteria, which were becoming recognized the world over as standing in etiological relation to the diseases of man and animals could also stand in analogous relation to those of plants. Of these earlier investigators Dr. Smith mentions as most important Burrill, Prillieux, Wakker and Comes, names relatively unfamiliar to the average student of bacteriology, who has limited his reading to that side of the subject presented in our text-books. It is interesting to note that the first of these, Burrill is an American, Professor of Botany in the University of Illinois, and that he established the bacterial origin of a disease known as pear blight, according to Dr. Smith, by investigations in the five years from 1878 to 1883. Of the others given special notice by the author, Prillieux, who proved that a disease of the wheat kernel was due to the growth of bacteria, is of French nationality, Wakker, who worked on a

yellow disease of hyacinths, was a Hollander and Comes who recognized "bacteria in the tissues of diseased plants as early as 1880," an Italian. Despite this early work plant bacteriology as a well ordered science, apparently lagged far behind its sister science, animal bacteriology, and even as late as the latter part of the decade from 1890 to 1900 there seems to have been a serious doubt in the minds of certain plant pathologists as to the exact relation of bacteria to plant diseases. The last few years have seen, however, a rapid and fruitful development of the subject until at the present time it must be recognized as of a magnitude and importance equal to that of animal bacteriology. In 1893 Dr. Smith began a careful systematic study of the bacterial diseases of plants in his laboratory in Washington and the two volumes thus far published may be said to represent some of the results of this work, although many of his experiments and conclusions have already been presented in contributions to various journals and society meetings. The first volume appeared in 1905. It is devoted to an exhaustive analysis of the literature, to detailed description of methods and technique, to accurate formulas for stains and media. In a word, it is essentially an elaborate introduction to the science of bacteriology and as such is extremely useful to workers in any of its branches. But a few diseases of plants are considered in this volume and these only to serve as illustrations for the general subject matter. Particular attention is paid to the discussion of classification, that of Migula being adopted. The treatment of such topics as nomenclature, morphological and cultural characters in relation to species identification is far more elaborate than obtains usually in our text-books. This of itself is of great value, especially to the student of the bacteria pathogenic for man and animals, whose chief interest has centered so long in determining the effects of microorganisms upon the animal tissues and who is apt to overlook the wide and interesting side of the subject represented by the botanist. Finally the bibliography in Volume I is most elaborate. It covers 63 pages and is arranged according to subject, but in chronological order. As arranged it is capable of serving as a constant source of information in general bacteriology. In Volume II Dr. Smith continues his subject by further notes on the historical development of plant bacteriology and by general considerations on the relationship of bacteria to

plant diseases. Such topics as the mode of infection of plants by bacteria are considered exhaustively and one can see the close analogy which holds between animal and plant bacteriology by noting the various channels which the author mentions through which bacteria infect plants, wounds for instance, natural openings, and stomata. Similar analogies can be observed by the facts which are brought out concerning the period of incubation which holds for plant diseases as well as for animal infections and in the treatment of the topic of germicides. These analogies, however, persist only to a certain point. Thus the rapidity with which bacteria infect plants depends upon conditions much more under the observation of the pathologist than in the case of animals. A juicy water-logged plant becomes infected far more quickly with a given organism than a dry, spongy specimen. In no instance can one explain so simply the variations seen in human and animal infections and we only confess our ignorance when we speak of heightened or lowered resistance. In other respects also the effect of bacterial growth upon plants is more easily explained by physical or chemical laws than with animals, as in those infections in which the invading organism secretes substances exerting a solvent action upon the cell wall, substances acting as enzymes and like enzymes destroyed by boiling and the action of chemicals. Indeed there are many phases in the reactions which occur between microorganisms and plant tissues which suggest interesting fields of speculation to the student of human disease. In certain respects the reaction which plants show towards bacteria differs essentially from the reactions seen in man and the animals, there being, namely, no production of antibodies in plants, the work already done along this line failing to reveal these bodies.

The subject of symbiosis is treated by Dr. Smith at considerable length and illustrated by an exhaustive description of the root nodules of the Leguminosae about which we have heard so often of recent years. In this condition an organism known commonly as *Bacillus radicola* or *Pseudomonas radicola* develops in the roots of plants like peas or beans and conveys nitrogen to them. Is this a true example of symbiosis, that condition in which two plants develop together, not antagonistic one to the other as in the case of parasites, but mutually helpful? This difficult question is discussed with great minuteness by Dr. Smith who concludes that the evidence thus far presented in regard to this much mooted case of true bacterial symbiosis is by no means conclusive and that much of the experimental work requires repetition and confirmation.

Such references as these indicate in general the scope of the first part of Volume II. The latter part of the volume is devoted to certain bacterial diseases of plants involving the vascular system, including a disease of cucumbers known as Cucumber Wilt, one of the cabbage termed Dry Rot or Brown Rot, and Wakker's bacterial disease of hyacinths or Yellow Slime. In each case the disease is carefully portrayed, the associated bacteria clearly and amply described and the experimental evidence given which has established the etiological relationship of the organism to the infection.

The two volumes are published by the Carnegie Institution of Washington, as a result of which more profuse and abundant illustrations are shown than in the ordinary text-book. The great value of the work, its thorough scientific character, the wealth of its bibliography all combine to make it a valuable addition to the library of the medical bacteriologist despite the fact that in its plan and scope it is designed especially for the plant pathologist.

W. W. FORD.

*Genito-urinary Diseases and Syphilis.* By HENRY H. MORTON, M.D. Illustrated. Third edition, revised and enlarged. \$5. (Philadelphia: F. A. Davis Company, 1912.)

The second edition of this book appeared in 1906, and since that date the spirochæta pallida has been discovered. In addition

much new work has come out on the prostate and tumors of the bladder, and most valuable new methods of treatment by the use of phenolsulphonephthalein, and salvarsan also have been put in practice. The results of all this work are incorporated in Dr. Morton's treatise, so that in its present form the book is modern, and may serve as an introduction to more comprehensive works on the same subject. Some of the illustrations are good, but many are so poor as rather to detract from than add to the value of the book.

*E. Merck's Annual Report of Recent Advances in Pharmaceutical Chemistry and Therapeutics.* Vol. XXV. 1911. (Darmstadt: E. Merck Chemical Works, 1912.)

These reports are valuable to the scientific pharmacologist and therapist, as they contain much information on newer drugs which it would be difficult to obtain otherwise without long search in many journals. In this number there are special chapters on the glycerophosphates, and digitalis glucosides and allied drugs. Those desirous of securing this report, can obtain copies for fifteen cents from Merck & Co., New York.

*Diseases of the Liver, Gall Bladder and Bile Ducts.* By HUMPHREY DAVY ROLLESTON, M.A., M.D. (Cantab.), F.R.C.P. Second edition. \$9 net. (London: Macmillan & Co., Ltd., 1912.)

Some years ago the writer had the pleasure of reviewing the first edition of this work. The favorable view which was then expressed has been fully supported by the best test of the value of a book—the extent to which it is used. This work has always proved a perfect storehouse of knowledge and has been of great assistance. A second edition is very welcome, especially as any work done by Dr. Rolleston is particularly satisfactory for the American reader, because he is so familiar with American literature and work. It has sometimes seemed as if he knew more about what was going on here than we did ourselves.

The general arrangement of the book is much as in the first edition. The first and largest part of the work is devoted to the diseases of the liver, after which those of the gall bladder and bile ducts are considered. Anatomical peculiarities and hepatosis receive very full consideration and are followed by the discussion of the diseases of the blood vessels including thrombosis and pyelophlebitis. The author has not changed his views as to the relative unimportance of functional disturbances of the liver, and it is probable that the public would be rather surprised if they could see the small space given to this subject in a systematic treatise. The subject of "biliousness" occupies a very small space and in this connection the author points out that symptoms so designated and often assigned to the liver are, as a rule, not due to primary failure on its part, but to disturbance elsewhere, particularly in the alimentary tract.

There is a clear description of the pericarditic pseudo-cirrhosis of the liver, a subject about which there is considerable confusion. The account given here seems extremely clear. Probably one turns to the subject of cirrhosis with the greatest interest, for there is no disorder so obscure in some aspects and so difficult to discuss in a clear and comprehensive way. As was said in the previous review, this is a very practical and satisfactory discussion of the subject. The description of the pathological changes is particularly good. There are many points in reference to cirrhosis about which we are in doubt. Take for instance the occurrence of ascites which in some cases appears to be a terminal event, in others due to a chronic peritonitis, sometimes local. The various possibilities are fully discussed. The important subject of syphilis of the liver receives adequate discussion.

Rarer conditions, such as actinomycosis, hydatid cysts, cystic disease, and primary malignant disease are thoroughly taken up. Secondary malignant disease receives a full discussion. To the



subject of jaundice a section is given, for although a symptom and not a disease, yet a special consideration of it is proper. The classification here given is into *extra-hepatic or obstructive* and *intra-hepatic, toxæmic or hæmo-hepatogenous*. These are subdivided in a most methodical way, there being no less than fourteen headings under the discussion of jaundice due to pressure on the bile-ducts from without. There are special sections on jaundice on the new-born, icterus gravis, infectious jaundice, and acute yellow atrophy. It is perhaps surprising to find how little space comparatively is required for the consideration of cholecystitis apart from cholelithiasis. This latter subject requires much more space and is thoroughly taken up. This section is an excellent example of what the discussion of such a subject ought to be. It is sufficiently full and at the same time not prolix. The summing up of the conditions which demand operation is excellent and a satisfactory statement of opinion on this subject, about which there is so much room for difference of opinion.

Altogether this work may be regarded as a model of what a treatise dealing with the diseases of a single organ should be. There is a proper balancing of various sections and a clear arrangement of heads and sub-headings which aids understanding so much. It is the best work on the subject which we have and is to be highly recommended. We desire to congratulate the author on the second edition.

*Health and Medical Inspection of School Children.* By WALTER S. CORNELL, M. D. Illustrated. (Philadelphia: F. A. Davis Company, 1912.)

Dr. Cornell has written a large work, which he divides into three main sections: 1, Medical Inspection; 2, Hygiene; 3, Defects and Diseases. As director of medical inspection of public schools in Philadelphia he writes from large experience, and his work is valuable. It would be more so were it not so comprehensive; to the first section, or Medical Inspection, which seems to us should be the most important one, the author gives only 150 pages; to Hygiene less than 50; and over 400 (!) to the defects and diseases of school children, and yet he does not pretend to be writing a medical treatise on these diseases. Exactly for what class of practitioners this book is intended is not clear. Both nurses, who are now so much and so profitably used for school inspection work, and young medical inspectors of schools will find special parts of it useful. The importance of the subject is now, it may be said, generally recognized and where medical inspection of schools is to be put in force for the first time, this book will prove a helpful guide in the hands of those who have to organize the work. It is somewhat marred by redundancy, and many of the illustrations are wretched—they are so small or so smudgy in reproduction as to be absolutely worthless. Innumerable photographs of children with adenoids are quite unnecessary, and those of skin lesions are not helpful. It is a pity such poor pictures should have been used. There are also certain statements made by Dr. Cornell in regard to contagious diseases, which need further support and evidence before they can be accepted as proven. The book is full of suggestions for those who have had little or no experience in this line of work, which covers a very broad field, and requires well trained physicians to fill the posts of school inspectors.

*Obstetrics. A Text-Book for the Use of Students and Practitioners.* By J. WHITEIDGE WILLIAMS. Third enlarged and revised edition. (New York and London: D. Appleton & Co., 1912.)

The popularity of this text-book, now published in a third edition, must be gratifying not alone to the author but to all who are interested in placing obstetrics upon a dignified, scientific basis—a position, it must be confessed, which has not been approached until the present generation. An increasing demand

for this work indicates that fewer and fewer teachers and practitioners are content with knowing how to care for patients at the time of labor and immediately thereafter. It is dawning upon those given charge over the training of medical students that interwoven with obstetrics are a number of sciences including not only embryology, histology, physiology, and pathology but also zoölogy, chemistry, and physics. The readers of this volume become familiar with the relation of these fundamental subjects to the science, and consequently to the rational practice of obstetrics.

In accord with his scientific attitude the author never hesitates to point out the gaps in obstetrical knowledge, but rather accepts these as an opportunity to encourage investigation. The student will also find in the numerous contributions of the author himself an incentive to undertake original work. Indeed it is the first-hand knowledge included in several of the chapters that makes them particularly attractive; especially is this true of the sections on the pelvis, the toxæmias of pregnancy, and puerperal infection.

The emphasis given the study of the pelvic outlet is justified because contraction of the outlet is somewhat more common than of the inlet, and also because serious dystocia may occur in cases of funnel pelvis. Generally, in these cases pubiotomy is the treatment of choice; this operation, when feasible, affords facility in the delivery and, furthermore, by permanently enlarging the pelvic cavity proves a curative measure. The treatment of labor with other types of contracted pelvis is clearly and logically discussed, greatly simplifying the problem of the management of such cases.

In contrast with the definite information regarding the pelvis, now placed at the disposal of the obstetrician, very little is known of the nature of autointoxication during pregnancy. The author maintains that finding different lesions in fatal cases we must believe there are several kinds of toxæmia of pregnancy, and insists that knowledge of these conditions will advance more rapidly if the pathological classification is adopted.

The author holds an uncompromising view of the responsibility of the doctor and the nurse in the aseptic management of labor. In fairness he cites the work of those investigators who have found pathogenic bacteria in the vagina during pregnancy; but to his mind it is not proven that these organisms may cause infection in the individual from whom they were obtained. The straight-forward statements which attribute the occurrence of infection to lax surgical technique in the conduct of labor will inspire resentment in anyone who is negligent of such details. But this teaching is certainly most wholesome, for it puts the obstetrician on guard; it is supported, moreover, by the best clinical and experimental evidence.

The entire book has been revised; not a single chapter has failed to undergo the alterations that were needed to bring it up to date. Thus, in the section on the development of the ovum we find incorporated what has been learned from the lately published descriptions of several early specimens. Yet, unfortunately, we still possess but meagre information regarding the formation of the fetal membranes in man; and, so long as it continues to be necessary to fall back upon the lower animals for a description of the development of the amnion and the chorion, this chapter will be a bewildering one for the medical student.

Practitioners wishing to keep abreast of the times will find this new edition very useful. Innovations in operative obstetrics, as pubiotomy and extra-peritoneal Cesarean Section, are critically discussed. The chapter on forceps is the most satisfactory that we have seen. The author's wide knowledge of the literature, his fairness in weighing evidence, and his clear, concise way of writing are qualities which have helped to give this volume a distinguished place among the text-books on obstetrics.

*A Treatise on Diseases of the Hair.* By GEORGE THOMAS JACKSON, M. D., and CHARLES WOOD McMURTRY, M. D. (Lea & Febiger, Publishers, 1912.)

The contents of this work have been gathered from text books on diseases of the skin, and from original articles on this subject. The reference bibliography given in footnotes, enhance the value of the volume.

While the text on the anatomy of the hair and hair follicle is a summary of dry facts, it is arranged in an interesting manner. Many illustrations, among which are six colored plates from Darier's work, give an adequate representation of the histological features of these structures.

The chapters on physiology and hygiene are written in a popular and entertaining way. Much good advice is given in regard to the ordinary care of the scalp, and this can be read with pleasure and profit by anyone.

The various diseases that are described, have been divided into four groups. Under "Essential Diseases of the Hair," are considered those peculiar to the hair alone. The second group comprise the "Inflammatory Diseases of the Hair Follicle." Next come the "Parasitic Diseases of the Hair." The "Diseases of the Hair Secondary to Diseases of the Skin" form the last group, and under this heading are described those diseases of the skin which may attack the scalp.

Unquestionably the most interesting chapters are those on ring worm and seborrhea. Sabouraud's work on these diseases has been fully abstracted. Many half-tone illustrations of the various forms of ringworm, with the cultural characteristics of the infecting fungus, are shown. His method of treating this obstinate disease with the Xrays, and of measuring the dose is also clearly demonstrated. Seborrhea capitis, too, is well described and illustrated. The formula for the culture medium, by which Sabouraud gets the best result in cultivating his microbacillus, is given, and also the directions for getting a pure culture of this bacterium.

The book should be welcomed heartily, as it is a valuable addition to our library on dermatological subjects.

*Hypnosis & Suggestion.* By W. HILGER, M. D. (Magdeburg.) Translated by R. H. FELKIN, M. D. \$2.50. (New York: Rebmam Company, 1912.)

This handbook of 224 pages opens with an introduction by Dr. Van Renterghem, of Amsterdam, who gives a brief but comprehensive survey of the rise and progress of psychotherapy during the last sixty years. A well-deserved tribute is paid to the memory of Liébeault, who, following up the work of Braid, introduced hypnotic treatment, as it is now used, into medical practice. The book is divided into four parts and deals with (1) nature and methods of hypnosis and suggestion; (2) suggestion and will; (3) influence of the will's action, suggestion, and various psychological factors in the disturbance of the area of sensation; (4) disturbances of the reflex activity and their treatment.

The book is written in a simple and clear way, but is rather superficial and unconvincing. Cases of alcoholism, morphinism, acute articular rheumatism, asthma, heart affections, retention of urine, constipation, etc., are reported which the author claims have been cured either by hypnosis, or by suggestion in the waking state.

Most of the cases reported, however, have been imperfectly analyzed, and there is very little account of the duration of the cures.

The author should be congratulated on being more honest than the majority of his confrères as he admits that, in the treatment of his cases by hypnosis or suggestion, he may employ hydrotherapy, dietetic measures, and drugs as occasion may demand.

*Selected Papers on Hysteria and Other Psychoneuroses.* By PROFESSOR SIGMUND FREUD. Translated by A. A. BRILL, *Journal of Nervous and Mental Disease*, Monograph Series No. 4. Second edition. (New York: 1912.)

It is exceedingly gratifying to think that sufficient interest has now been aroused in Freud's works to warrant a second English edition of Brill's able translation. The chapters are taken from three different volumes of Freud's works, and have been so selected that one can get an excellent idea of his views in regard to hysteria and the other psychoneuroses. The technique of the treatment of these cases by means of psycho-analysis is fully dealt with, and numerous cases are reported, some of which are gone into in detail so that one sees just how the technique is utilized. There is absolutely no doubt but that Freud has been able to shed much new light on the psychoneuroses, and by means of psychoanalysis one can get to a point where some of the curious manifestations of these states can be understood and frequently explained. He believes that hysterical symptoms are the symbolic expression of the realisation of a repressed wish, and serve as a source of gratification to the patient. These symptoms can be made to disappear, and will not return if one is successful in thoroughly awakening the memories of the causal process with the accompanying affect, and if the patient can be got to thoroughly discuss the process and give free play to the affect. When these views were first promulgated a great many physicians jumped to the conclusion that by means of psychoanalysis the whole constitution of the individual could be changed, but Freud has stated specifically that one must rest content if he can remove the disease for which such a constitution shows a tendency, and that he must not hope or expect to be able to change the constitution of the individual.

One of the most frequent objections which one hears in regard to psycho-analysis is that in certain cases there is a great danger of suggesting things which may be harmful to the patient. To that objection Freud replies by saying that it is not possible to press upon the patient things which he apparently does not know, or to influence the results of the analysis by exciting expectations.

Great emphasis is laid upon the analysis of dreams—both "day dreams" and night dreams—as they give the most direct access to the unconscious. No case can be adequately treated without an investigation of the dream states.

With most of Freud's general principles one must be in entire agreement and certainly a tremendous impetus has been given to the study of the psychoneuroses by his views, but one hesitates to accept all his ideas and theories in regard to the rôle of infantile sexuality especially as most of his deductions are drawn from the "fancies" and "reminiscences" of psycho-neurotic individuals.

Another matter that may be criticised is the fact that he tends to draw very sharp distinctions between various psycho-neurotic states, for instance between neurasthenia and the anxiety neuroses. Neurasthenia is characterized "as a monotonous morbid picture in which as shown by analysis psychic mechanisms play no part," whereas the anxiety neuroses are said to have a very strongly marked sexual etiology. His proofs of anxiety neuroses being a separate disease entity are not especially convincing, and his last argument is distinctly weak, e.g. "if the separation of anxiety neurosis from hysteria be denied one will also be unable to maintain the so painstakingly acquired distinction between neurasthenia and hysteria, so indispensable for the theory of the neuroses."

Two further chapters are added in this second edition to those contained in the first, one on "Wild" Psycho-analysis in which it is proved to be exceedingly important to thoroughly learn the technique of psycho-analysis; and the other on "The Future Chances of Psycho-Analytic Therapy."



*Building a Profitable Practice: Being a Text-Book on Medical Economics.* By THOMAS F. REILLY, M. S., M. D., etc. (Philadelphia and London: J. B. Lippincott Company, 1912.)

Dr. Reilly's book will doubtless be popular and have a large sale, for it contains instruction on many points about which the young practitioner, when leaving the medical school, is usually in ignorance. But we cannot commend it. Its tone is lacking in dignity on many important questions of ethics, and the standards of the medical profession would not be raised were this work its only guide. The rules of practice, as laid down by the author, will help the beginner to make his way financially, but they are not such as to give him high ideals or make him feel that in the practice of medicine there is a higher and finer end to be attained than a well-filled pocket book.

*Infant Feeding.* By CLIFFORD G. GRULEE, M. D., Assistant Professor of Pediatrics at Rush Medical College. Illustrated. \$3. (Philadelphia and London: W. B. Saunders Co., 1912.)

The book, "Infant Feeding," of 295 pages, is based on a course of lectures given to the students of the Rush Medical College. In it the author aims to combine the knowledge of the scientific processes which underlie infant feeding in such a way that they may be applied in an efficient manner by the practising physician.

The volume comprises four main divisions: Part I relates to the "Fundamental Principles of Infants' Nutrition"; Part II, to the "Nourishment of the Infant on the Breast"; Part III, to "Artificial Feeding"; and in Part IV "Nutrition in other conditions" is considered.

Much of the work is a compilation of facts which may be found in other text-books on this subject, and, for that reason, a summary in detail is not necessary. The importance of breast feeding is properly emphasized. The injunctions given apropos of the promiscuous and unthinking use of proprietary foods are admirable, and the advocacy of longer intervals between feedings is in the trend of modern thought.

While the views in general accord with the opinions held by those most actively engaged in teaching pediatrics, exception may properly be taken to certain views therein expressed. For example, in Part III, Chapter 12, "Nutritional Disturbances of the Artificially Fed Infant," the attempt clearly to classify these disorders is made. The grouping which is advocated is based partly on the classification suggested by Czerny and partly on that laid down by Finkelstein. The shortcomings of such a classification are best emphasized by the grouping of ileo-colitis, cholera infantum, dysentery, etc., under "Intoxication," conditions which are clinically dissimilar, even widely differentiated, with known pathological and etiological differences. Such a classification is complicated and inaccurate, and is to be condemned from both a scientific and practical standpoint. The disregard also of the streptococcus in milk as a direct infecting agent (page 113) is unwise, a fact indicated by the recent epidemics of "Septic Sore Throat."

The Bibliography is an asset of value to the book, and the index is complete. The author appreciates the value of illustrations; some of these are excellent, while others, especially those of the stools, are very poor.

*Anesthetics and Their Administration.* By SIR FREDERIC W. HEWITT, M. V. O., etc. Fourth edition. Illustrated. \$5. (London: Macmillan & Co., Ltd., 1912.)

There are few problems that come to the anesthetist that are not discussed in this revised edition. The discussion of the theoretical and experimental physiology of anesthesia are especially interesting and instructive, and the author also offers suggestions for further investigations. He is very conservative in the conclusions he draws from the experimental work. The

individual variation of patients has so much to do with the administration of an anesthetic that it is very difficult to give rules or to describe any method of procedure that will apply to all for the administration of an anesthetic. This phase of the subject has been handled very skillfully. Some of the newer methods of administration which are not yet thoroughly established are merely touched upon, e.g., intratracheal insufflation is dismissed with one paragraph. Two new chapters have been added in this edition, one on local and regional anesthesia, the other on medico-legal aspects of surgical anesthesia. The book is well written and illustrated. It is complete, without being too cumbersome, making it useful both for the student practitioner and special anesthetist.

*A Laboratory Hand-Book for Dietetics.* By MARY SWARTZ ROSE, Ph. D. \$1.10. (New York: The Macmillan Company, 1912.)

This is an excellent work, one that should prove most useful to nurses as well as doctors. Dr. Rose has compiled many tables showing the nutritive value of a great variety of foods. With these tables it is easy for anyone to calculate a food value and requirement for any person at almost any age and to prepare a suitable dietary under a doctor's order. The tables are prepared not only with the weight in pounds and ounces but also in grams, but the average price of the articles is given, so that the cost of the dietary is readily computed. The caloric value of the foods is also tabulated. In addition to the tables Dr. Rose has also prepared problems to be worked out, so that this hand-book is most instructive, and to be warmly commended as a clear exposition of a difficult problem.

*Progressive Medicine.* Edited by HOBART AMORY HARE, M. D., assisted by LEIGHTON F. APPLEMAN, M. D. Vol. IV. (Philadelphia and New York: Lea & Febiger, December, 1912.)

Except for two chapters—Practical Therapeutic Referendum and Surgery of the Extremities, Shock, Anaesthesia, Infections, Fractures, Dislocations and Tumors—the entire volume is given over to the discussion of surgical problems dealing in large part with the abdominal and pelvic organs. The contributors are Bloodgood, Bonney, Bradford, Goodman and Landis, who furnish excellent résumés of the progress in the treatment of these various affections. This volume is valuable in giving the reader the views of leading operators all over the world on various difficult surgical problems.

*Elementary Bacteriology and Protozoology.* By HERBERT FOX, M. D., Director of the William Pepper Laboratory in the University of Pennsylvania. (Philadelphia and New York: Lea & Febiger, 1912.)

This little book is written primarily for the beginner in bacteriology and for the nurse, to give, as the author states, an "idea as to the world's economy especially in disease." The subject matter is carefully selected, the text is well prepared and the important pathogenic organisms described with accuracy although briefly. The book will doubtless serve a useful purpose in instruction in elementary bacteriology.

*Principles of Microbiology. A Treatise on Bacteria, Fungi and Protozoa Pathogenic for Domesticated Animals.* By VERANUS ALVA MOORE, Professor of Comparative Pathology, Bacteriology and Meat Inspection, New York State Veterinary College at Cornell University and Director of the College. \$3.50. (Ithaca, N. Y.: Carpenter & Co., 1912.)

Seldom if ever has a text-book on bacteriology appeared in the English language which offers so much to praise and so little to criticize as this publication from the pen of Professor Moore.



Dedicated by him to those students who have worked under him in his own laboratory, it may well have been dedicated to all students of bacteriology regardless of whether they are interested in the medical or the veterinary sciences. Indeed the essential principles of bacteriology, its methods and technique are the same in all its branches while in addition the historical development of the science and its gradual evolution from chaos to clearness is indissolubly bound up with the investigations into the life history of microorganisms which cause diseases in animals. It is natural, of course, that in a book designed particularly for veterinary students certain diseases will be emphasized which seldom are touched upon in text-books upon the bacteria pathogenic for man. In many cases, however, these organisms are the ones most carefully studied in courses of bacteriology in medical schools and form a chief part of the armament of the teacher of this subject. More than a third of the book is given up to a consideration of the general principles of bacteriology and such topics as the isolation and cultivation of bacteria, methods of examination of cultures, microscopic study of specimens and the vital activities of bacteria are treated at length. Methods and technique indeed are emphasized throughout, but possibly the features which are of the greatest value in this book of Professor Moore's and in which it is superior to other text-books is the care and thoroughness which are devoted to descriptions of the various microorganisms such as the *Streptococcus pyogenes*, the *Micrococcus aureus*, the *Bacterium anthracis*, the *Bacterium mallei*, the *Bacillus lactis aerogenes* and the tubercle bacillus. Particularly to be praised is the author's treatment of the organisms causing hemorrhagic septicemia in animals, a chapter in bacteriology in which the majority of our text-books are either hopelessly muddled or entirely inadequate. The actual number of organisms described is somewhat small and this may excuse the author for not mentioning the *Bacillus aerogenes capsulatus* of Welch and Nuttall, the most widely distributed anaerobic organism in nature. The chapter on protozoa is rather short, but considering the fact that the book has less than 500 pages the space devoted to this subject represents probably as much as the author felt could be allowed. The classification adopted for the protozoa is practically that of Calkins, the classification for the bacteria being that of Migula. The discussion of filtrable viruses also seems scanty when we think of the importance of the subject and remember the classic investigations of American bacteriologists upon that widely distributed disease, hog cholera. The treatment of specific bacterial products is exceptionally good, excellent descriptions being given of the precipitins, and agglutinins, and the opsonins. The final chapter of the book on Immunity and Vaccine Therapy is very brief, but this may be an advantage in view of the long and complicated discussions of the subject in other text-books.

This book of Professor Moore's is most highly to be recommended to all students of bacteriology, and especially to new workers in this field who desire to acquaint themselves with the fundamental elements of the subject.

*The Chemic Problem in Nutrition (Magnesium Infiltration).* By JOHN AULDE, M.D., etc. Illustrated. (Philadelphia: John Aulde, M.D., 1912.)

The author has strayed into many fields of science more or less unfamiliar to the practicing physician and apparently unfamiliar, at least in part, to himself. Many of his historical statements and verbatim quotations are correct. However, his use of periods instead of interrogation marks at the end of innumerable sentences is much to be regretted. Illogical deductions instead of scientific proof as well as incomprehensible statements characterize the book throughout. There is no excuse for the body of the publication.

L. G. R.

*Die Experimentelle Pharmacologie als Grundlage der Arznei-behandlung.* Von DR. HANS H. MEYER UND DR. R. GOTTLIEB. (Berlin-Wien: Urban u. Schwarzenberg, 1911; New York: Rebmman Company.)

The second edition of this most admirable text-book deserves a good deal of attention. In the first place, the subject is presented in a very original way, in as much as the drugs are classified according to the anatomical structures upon which they act. In the chapter of the pharmacology of the heart, drugs are described, which exhibit cardiac action. This scheme of presentation has a great many advantages over the one commonly found in text-books of pharmacology. A physician dealing with a specific pathologic condition will find it easy to familiarize himself with the details of the action of the various drugs which might come into consideration. The student will find much inspiration in this book, and it may well be said that to the pharmacologist it gives a great deal of pleasure. This text-book undoubtedly presents the best known scientific basis for the therapeutic use of drugs. It is to be hoped that an English edition will appear in the near future.

*Nachweis und Bestimmung von Giften Auf Biologischem Wege.* Von DR. H. FÜHNER. \$2.25. (Berlin-Wien, Urban & Schwarzenberg, 1911; New York: Rebmman Company.)

This practical guide for the detection and estimation of organic and inorganic poisons deals with the biological methods which are used in pharmacologic and toxicologic work. In a clear and elementary way, methods are described in detail for the determination of the antiseptic action of drugs, the standardization of digitalis, epinephrine, local and general anesthetics, antipyretics, thyroid and the detection of muscarine, strychnine, veratrine, curarine, nicotine, salicylic acid, etc. Various cells of vegetable and animal origin serve as test objects. Numerous illustrations are inserted into the text and help to make the methods very comprehensive. This book is primarily intended for use by toxicological chemists and physicians who have to deal with medico-legal cases. The author remarks in the preface that the known methods are relatively few in number, and that some of them are not yet worked out thoroughly. In spite of these deficiencies we believe that the author can be congratulated on his efforts.

*Manual of Medicine.* By A. S. WOODWARD, M.D. \$3.75. (Edinburgh, Glasgow and London: Henry Frowde and Hodder & Stoughton, 1912.)

Dr. Woodward says in his preface that he hopes to fulfill a two-fold purpose with this book: that of supplying a *vade mecum* for the student clerking in the wards or out-patient department, and a convenient reference for the busy practitioner. We hope, in spite of our dislike for such manuals, that the author's desire may be fulfilled to his own satisfaction. It is a manual which would be of service to nurses also. The author has condensed the larger text-books of medicine satisfactorily, bringing out the main points of each disease, but medicine cannot be served up in this way any more than its sister, surgery, and be really helpful to a young practitioner who wants to advance. He had better search the larger text-books than refer to the primers of the subject he is studying.

*Stuttering and Lipping.* By C. W. SCRIPTURE, Ph.D., and M.D. \$1.50. (New York: The Macmillan Company, 1912.)

It is only within a few years that doctors have studied stuttering and lipping scientifically, and this book is the product of such study. It is unfortunately true that few physicians have the necessary patience and time to give to patients suffering from these troubles, and the poor stutterer, as a result, often enough

has a miserable time in life. Dr. Scripture's book will fill a long felt want, for it is but a small manual which any interested physician can easily master in a short time, and an intelligent patient can also gain much from a careful perusal of it. The author, who has been for some years a special student of these conditions, describes stuttering as a psychoneurosis, and the best methods of treatment, and divides lispings into three forms—negligent, organic, and neurotic—and gives a long list of exercises to overcome this disturbance of speech. The book has been carefully and well prepared, and may be warmly commended.

*Fiske Fund Prize Dissertation No. LV. Medical Inspection of Schools.* By ALLEN G. RICE, M.D. (Providence: Snow & Farnham Company, Printers, 1912.)

This dissertation is an interesting review of the development and growth of medical school inspection in this country. The author has gathered much information as to how the schools are inspected, and how parents and boards of health are notified when children are ill, and his essay is of value to a large body of physicians who take an interest in this branch of civic welfare.

*Year Book of the Pilcher Hospital.* No. 2. (Philadelphia: J. B. Lippincott Company, Philadelphia, 1912.)

The second year book of the Pilcher Hospital is an interesting production. Some of the papers are quite brief, so that the volume is not large, but well worthy of note as an expression of the excellent work done in this hospital. Many of the papers are illustrated. The articles are classified under the following headings: Fractures, cancers, benign growths, affections of the digestive organs, urological cases, not classified, and appendices with twelve subjects reported on. The wealth of material of the staff, which is composed of only three operators is great; and such a volume as this shows how much could be done by others if they would only take the same trouble as the Pilchers to publish their records—for records of private cases often are of as much value as those from public hospitals. The Doctors Pilcher are to be heartily congratulated on their Year-Book from every point of view.

*A Practical Medical Dictionary.* By THOMAS LATHEROP STEDMAN, M.D., etc. Second Revised Edition. Illustrated. \$5.00. (New York: William Woodard Company, 1912.)

The second edition of this excellent dictionary appears within about a year of its first publication, showing the well-merited appreciation it has received from the medical profession. In its present form it contains 2000 more words than in the original, but its general appearance remains the same; and it is a pleasure to have the opportunity to recommend it anew.

*X-Ray Diagnosis and Treatment.* Review of Drs. BYTHELL and BARCLAY's book.

The simplicity and concise manner in which this book is written should make it especially valuable to the student and general practitioner.

It is very gratifying to find a book which is so largely devoted to the fundamental principles of interpretation of X-Ray shadows.

Probably the weakest part of the book is that devoted to head and sinus work. Stereoscopic radiography of all head cases taken at one or two good constant angles will obviate the extreme distortion produced by angulation for certain difficult parts.

The author's interpretation of early phthisis seems a little exaggerated, remembering that various other infections as chronic influenza and low grade pneumococcus will give practically the same radiographic picture.

The chapters on oesophageal stenosis, and stomach and intestines are especially good.

More or less divergence of opinion is, of course, to be expected in such a rapidly developing field as radiography. Dr. Bythell and Dr. Barclay have given us their opinions and experiences, and to them we are greatly indebted.

On the whole one can regard this book as a most worthy addition to the literature on radiology. C. A. WATERS.

*Life of Sir William Tennant Gairdner, K.C.B., M.D., LL.D., F.R.S., Regius Professor of Practice of Medicine in the University of Glasgow.* By GEORGE ALEXANDER GIBSON, M.D., Sc.D., LL.D.; Senior Physician to the Royal Infirmary, Edinburgh. (With a selection of papers on general and medical subjects. (Glasgow: James Maclehose & Sons, Publishers to the University, 1912.)

Rather more than one-third of this handsome volume of 817 pages is devoted to the life and career of Sir William Gairdner and the remainder is devoted to judicious selections from his papers on general and medical topics.

The story of his life is given very judiciously in a series of chapters arranged somewhat differently from usual biographies. We are told of his early life, his hospital and medical training, his life in Glasgow, his marriage and family, his university and hospital labors, his medical and scientific work, his political, theological, and religious views, and his personal character.

His life is presented to us not so much chronologically as topically, and the reader is able to view it as a whole and to estimate his achievements. He unquestionably possessed a mind of no ordinary scope, both as a clinician and as an original investigator. He had broad views of the relation of medicine to science. He worthily expressed this in his declaration that "the true art of medicine is that it is doubly founded, first on experience and then on reasoned experience." He constantly reiterates that to know medicine one must have "the knowledge of things as opposed to words and abstract ideas." He did not ask for a hasty diagnosis but for a thorough one. These principles are especially applied in his papers on purely medical subjects, several of which are printed in the volume. They are models of clear thinking and accurate presentation and deserve careful reading now, although some of them were written a half century ago.

He was a skillful clinician, a painstaking teacher, an efficient public health officer, and a ready writer. He had the devoted affection of pupils and colleagues, and the confidence of the public.

An interesting account is given in the volume of his visit to America in 1891, and some letters are printed containing personal references to Pepper, Holmes, Weir Mitchell, Osler, the Bowditches, and others whose names are familiar. He was not critical, but appreciative, and showed everywhere the same child-like spirit and keen interest in what he saw which characterized his home life.

The book contains many pleasant anecdotes, some of which, especially those as to his absent-mindedness are not unfamiliar. It is most interesting and deserves to be read by physicians.

*The Anatomy of the Human Eye.* Illustrated by Enlarged Stereoscopic Photographs. By ARTHUR THOMPSON, M.A., M.B., F.R.C.S. (Oxford: At the Clarendon Press, 1912.)

The study of the anatomy of the eye by means of stereoscopic pictures is a welcome change from the study of the anatomy by means of the usual text, and the accompanying diagrams and pictures, which have, in many instances, been reproduced for years in the newer and older text-books. This is an entirely new set of pictures to the number of sixty-seven, with a carefully written description of each one, and the work marks a distinct step forward in the make up of ophthalmological text-books and



atlases. This series of plates enables one to see anatomical details at a glance, without effort on the part of the imagination to supply the perspective. The pictures are carefully accurate, and are not overdrawn for the sake of effect. Most students must view such pictures with real interest, and a vivid impression will be left on their minds which pages of reading matter might hardly as effectively accomplish.

The painstaking care and work on the author's part deserves the grateful appreciation of all readers of ophthalmologic literature, and a work such as this should be a lasting monument to the wisdom of the accomplished author. We heartily commend this work to anyone taking up the study of eye diseases, and assure him that he will be repaid manifold for the slight trouble which the use of the stereoscope will necessarily require.

We hope that this work will be handily available in all clinics where medical students are instructed in ophthalmology; for by means of it many rough paths on the part of instructor and student will be smoothed over, and the efforts of each very much lessened.

B. B. BROWNE, JR.

*Scientific Memoirs.* By OFFICERS OF THE MEDICAL AND SANITARY DEPARTMENTS OF THE GOVERNMENT OF INDIA. (Calcutta: Superintendent Government Printing, India, 1912.)

*New Series No. 51. A Streptothrix Isolated from the Spleen of a Leper.* By MAJOR W. G. LISTON, M.D. and CAPTAIN T. S. B. WILLIAMS, I.M.S. 1/4.

*No. 52. Dysentery in Hazaribagh Central Jail—January, 1910-March, 1911.* Being the Report of an Inquiry Carried out by CAPTAIN R. T. WELLS, M.B. 2/9.

*No. 53. The Development of the Parasite of Indian Kala Azar.* By CAPTAIN W. S. PATTON, M.B. 1/2.

The first of these three reports is a very brief study by Major Liston and Captain Williams of a new (?) streptothrix. The growth of the organism on lemco-agar is well described, and there are some beautiful colored micro-photographs which demonstrate its morphology finely.

Captain Wells has added another interesting chapter to the study of dysentery, which is so frequently obscure in its causative, and laboratory workers will find this memoir well worth careful consideration.

The third paper, by Captain Patton, also illustrated by a fine photogravure plate showing the development of the parasite of kala azar, is another one of those important contributions coming from the medical officers of the English army stationed in India. Few of these scientific contributions will have many readers, but special workers must have these publications close at hand, since they throw light on many questions which are still unsolved.

*Oxford Medical Publications: Pathology of the Eye.* By P. H. ADAMS, M.B., etc. \$1.50. (London: Henry Frowde, and Hodder & Stoughton, 1912.)

This little book may doubtless be found of value to those who may wish to rapidly look up pathological points about the eye; for it is a convenient little handbook. It is probably a little too concise, and in many places the reading matter suggests a too brief discussion, when often cold facts are stated and then left to stand without further amplification. For the scientific reader this volume will have but little value.

Had the author, wishing to keep his volume small, devoted more specific attention to the consideration of lesions which are peculiar to eye tissues, and allowed less space to the study of inflammations which follow the same course in the eye as they do in other tissues, he would have produced a volume of more interest. The study of the eye changes met with in Glaucoma, and the consideration of the aetiological pathological factors involved in cataract and sympathetic ophthalmitis are insufficient for any

comprehensive understanding of the subject. The book limits itself to the pathology of clinical cases, no attention being given to experimental pathology. In a word, the material of this work is readily available in some of our larger text-books on the eye, and it deserves specific approval only as a convenient little volume.

B. B. BROWNE, JR.

*Oxford Medical Publications: Kidney Diseases.* By W. P. HENINGHAM, M.D., etc. With Chapters on Renal Diseases in Pregnancy. By HERBERT WILLIAMSON, M.D., etc. \$5.50. (London: Henry Frowde and Hodder & Stoughton, 1912.)

This is one of the best of the Oxford Medical Publications, and is especially interesting as being largely the result of the author's work in his own wards and hospital. It is not, as many other text-books, mainly the output of others. Dr. Heningham acknowledges his indebtedness to the labors of other writers, but throughout this book we feel that we are getting the personal views and conclusions of the author, and this makes it well worth reading. It is an excellent book for students. Dr. Heningham deals with the obscure origin and development of chronic nephritis in a broad manner, and does not attempt to classify too finely the different types of chronic nephritis either from a clinical or pathological standpoint. Of other diseases of the kidneys he gives a capital clear picture, one drawn from large bed-side experience. The author possesses unusual gift of style which makes his presentation of the subject most attractive. We only wish the case histories were in a smaller type than the body of the book.

*A Manual of Auscultation and Percussion.* By AUSTIN FLINT, M.D., etc. Sixth Edition, Revised and Enlarged. By HAVEN EMEYSON, M.D. \$2.00. (Philadelphia and New York: Lea & Febiger, 1912.)

One of the best of manuals, it is well that it should be constantly presented afresh to students. The late Austin Flint was one of America's few great physicians and his work on the lungs and heart marked an epoch in American medicine. His contributions are not as well known as they should be by the rising generation of young physicians, most of whom know his name only in connection with the murmur of aortic insufficiency, but his studies of the lungs are more important. Every student should study this manual with care, for Flint's method of presentation is exceptionally good, and once having obtained a mastery of the underlying principles as enumerated by him, the student will not find the diagnosis of conditions within the thorax so difficult as he is apt to do. There are only the classics which are ever fresh, and this manual may be justly regarded as one of them.

*The Course of Operative Surgery. A Hand-book for Practitioners and Students.* By PROF. DR. VICTOR SCHMIEDEN, Berlin. Second Enlarged Edition. Translated and Edited by ARTHUR TURNBULL, M.B. (Glasg.). \$4.00. (New York: William Wood and Company, 1912.)

This is the first American edition of Schmieden's Surgery, but it corresponds exactly to the second and latest German imprint. It is one of the briefest manuals of surgery that has lately appeared, and should on this account be welcome to a large body of students. It is well and abundantly illustrated. Its brevity is due to the fact that the author describes only the main operations, so that the student is not overwhelmed by a mass of details. With a solid foundation in surgery based on a thorough knowledge of anatomy it is not difficult for a young surgeon to meet conditions as they present themselves, and he does not require all operations to be described in book form. Watching operators he can learn much that he could never acquire from



books, and if he has mastered the principles as set forth in this work he will have a firm base to build upon. This is, therefore, a more serviceable book for him than many larger treatises.

*New Aspects of Diabetes. Pathology and Treatment.* By PROF. DR. CARL VON NOORDEN, Vienna. \$1.50. (New York: E. B. Treat and Company, 1912.)

A work by von Noorden on Diabetes must be of interest to all clinicians, since he is famous for his profound studies in this disease. The matter in this small volume was delivered in a course of lectures at the Post-Graduate Medical School of New York. The presentation of some of the underlying problems in this mystifying disease is excellent. He discusses the source of sugar, the rise in caloric production and its causes, the control of sugar formation and its disturbances, the theory and therapy of diabetes, and acetonuria with its influence on the treatment of diabetes mellitus. For physicians and students who are not acquainted with the latest work on this disease these lectures will aid largely to keep them informed on the modern trend of thought in regard to the chemical questions involved in this disturbance of metabolism.

*Nutritional Physiology.* By PERCY GOLDTHWAIT STILES. (Philadelphia and London: W. B. Saunders Company, 1912.)

The author is professor of physiology in Simmons College, and his small treatise is evidently intended for such classes of students as he has there; that it is not intended for those who mean to study medicine seriously as a profession, but rather for those who desire and need a thorough grounding in the principles of the subject and for this class it is a good book, a clear presentation of the process of digestion. The author is to be congratulated on his success in dealing with a difficult topic in an interesting manner; and he has shown his skill in eliminating what was not essential to a satisfactory explanation of the topic.

*Practical Physiological Chemistry.* By PHILIP B. HAWK, M.S., Ph.D. Fourth Edition, Revised and Enlarged. \$2.50. (Philadelphia: P. Blackiston's Son & Co., 1912.)

With a few additions necessitated by the latest work on enzymes, carbohydrates, proteins, blood, etc., that has appeared since the third edition of this work in 1910, the book maintains all its good characteristics which have made it popular with students. Dr. Hawk's work is well planned and written.

*The People's Medical Guide.* By JOHN GRINSHAW, M.D., etc. \$3.00. (New York: The Macmillan Company, 1912.)

The sub-title for this work reads: *Points for the Patient, Notes for the Nurse, Matter for the Medical Adviser, Succour for the Sufferer, Precepts for the Public.* This makes one feel as though one had gone back half a century or more when such guides were common, but which little by little have disappeared, so that no longer in the home along side of a bible, a photographic album and a book of verse, on the center table in the parlor is a medical guide and counsellor to be found. On the whole the disappearance of such books can be looked on with approval, but there are parts of the world where unfortunates are bound to dwell and to whom such a book as this may be a god-send. Dr. Grinshaw in his volume of over 800 pages has put a mass of useful information on many matters in such a way as to be really serviceable for the class for whom it is intended. To compile such a work is no easy task, and the author has done it with ability. He divides his subject into two sections on medicine, one on surgery, one on diseases of special organs, one on skin diseases,

one on food and feeding and one on physical exercises, so that the medically uninformed reader may easily find what he wants. He writes in an easy, familiar, not too technical style, as a doctor should talk to his patients, and throughout he shows common sense. For intelligent people who are travelling in remote regions far from medical aid of any sort this volume would be a really valuable one for them to carry along. It is also a work which many a nurse would find often helpful.

*Consumption in General Practice.* By H. HYSLOP THOMSON, M.D., D.P.H. (London: Henry Frowde and Hodder & Stoughton, 1912.)

The book is a clear and brief presentation of the fundamental principles of the diagnosis, prognosis and treatment of pulmonary tuberculosis. It is intended for the general practitioner and is written in a direct, elementary style with no display of erudition. It is the expression of the experience of one man, not a coalition of the opinions of many men. What is thus lost in range and detail is gained in concreteness and force. The book will therefore be useful and stimulating to many without the leisure or inclination to study the subject thoroughly. There are some statements that will not receive general accord; for instance, that "at any time in the course of miliary tuberculosis the tubercle bacillus may be demonstrated in the circulation"; others that to the initiated are evidently errors, but errors that may occasion serious consequences if literally followed; for instance, that the initial dose of tuberculin for diagnosis is 0.1 cc. As is usual in treatises on tuberculosis the paragraphs dealing with the use of tuberculin in diagnosis are the poorest in the book. The directions for its use are insufficient, some of the directions are faulty and the interpretation of the results of the tests unsatisfactory.

L. H.

## BOOKS RECEIVED.

*Studies from the Rockefeller Institute for Medical Research.* Reprints. Volume XV. 1912. 8vo. New York.

*Progressive Medicine.* A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M.D., assisted by Leighton F. Appleman, M.D. Volume III. September, 1912. 8vo. 253 pages. Lea and Febiger, Philadelphia and New York.

*A Manual of Pharmacy.* By M. F. DeLorme, M.D., Ph.D. Third edition, with 19 illustrations. 1912. 12 mo. 221 pages. P. Blackiston's Son and Co., Philadelphia.

*Manual of Chemistry.* A Guide to Lectures and Laboratory Work for Beginners in Chemistry. A Text-Book Specially Adapted for Students of Medicine, Pharmacy and Dentistry. By W. Simon, Ph.D., M.D., and Daniel Base, Ph.D. Tenth edition, thoroughly revised. With eighty-two illustrations, one colored spectra plate, and eight colored plates representing sixty-four chemical reactions. 1912. 8vo. 774 pages. Lea and Febiger, Philadelphia and New York.

## NEW PUBLICATIONS.

The following three monographs:

**Free Thrombi and Ball-Thrombi in the Heart.** By J. H. HEWITT, M.D. Price, \$1.00.

**Benzol as a Leucotoxin.** By LAURENCE SELLING, M.D. Price, \$1.00.

**Primary Carcinoma of the Liver.** By M. K. WINTERNITZ, M.D. Price, 75 cents.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore. Other monographs will appear from time to time.



# BULLETIN

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## TUBERCULOSIS OF THE URINARY SYSTEM IN WOMEN.\*

### REPORT OF A CASE.

By EDWARD H. RICHARDSON, M. D.,

*Associate in Gynecology, The Johns Hopkins University.*

The purpose of this communication is to present a brief summary of the present-day knowledge of urinary tuberculosis in women, emphasizing especially the possibility and importance of an early diagnosis of this affection. The distressingly large proportion of advanced cases of renal and bladder tuberculosis encountered in every urological clinic renders it sadly apparent that there is more urgent need of familiarity with facts already established concerning this disease than for stimulating further research into its unsolved problems.

Authorities are now pretty generally agreed that the vast majority of cases occurring in women represent blood-borne infection from some other focus in the body—situated, it may be, in the lungs, lymph glands, joints, intestines or elsewhere—which first attacks the kidney and later descends to involve the ureter and bladder secondarily. Primary tuberculous infection of the female bladder through the urethra, if it occurs at all, is exceedingly rare. The same may be said of hæmatogenous bladder infection. An occasional case occurs through direct extension from some nearby focus, as in the fallopian tube, the hip joint, the spine or the bowel; but in these cases the involvement of the urinary system is a late complication. The question of ascending renal infection along the ureter

from a bladder focus has long been a favorite topic of energetic controversy between both clinical and experimental observers of large experience. A few loyal and uncompromising champions of this view still maintain that it is of frequent occurrence, especially with reference to involvement of the second kidney. Most observers, however, hold that while this is a theoretical possibility which now and then materializes, it is certainly exceptional in women, and that most of the reported cases admit of more rational interpretation on the assumption of independent hæmatogenous infection.

There are two forms of renal tuberculosis—the *acute miliary*, and the *chronic localized*.

The former is of no clinical significance, since it is but part of a generalized systemic tuberculosis, probably resulting from widespread dissemination of the bacilli through the blood as distinguished from the embolic mode of infection.

Of the chronic localized form various classifications, based upon the pathological anatomy, have been suggested. For practical purposes it is sufficient to differentiate three main types. (1) The *massive*, caseous, or ulcerative—by the older writers happily styled *renal phthisis*. Here the organ becomes converted into multiple cavities which may communicate with the kidney pelvis, are separated from one another by septa of disintegrating renal or fibrous tissue, and filled either with

\* Paper read at a meeting of the Johns Hopkins Hospital Medical Society, January 6, 1913.

soft caseous or curdy necrotic material. This may go on to complete destruction of the parenchyma. The capsule and perirenal tissues not infrequently become involved, leading to extensive infiltration or abscess formation. If the ureter becomes permanently obstructed before the secretory portion of the kidney has been fully destroyed, tuberculous pyonephrosis results. Finally, the destructive inflammation may open a branch of the renal vein and lead promptly to general miliary tuberculosis.

(2) The second variety begins in the pyramids and leads to ulceration of the apices of the papillæ with hæmaturia as an early symptom.

(3) Then there is a third variety in which the kidney is studded with numerous firm grayish-white nodules varying in size from one to three or four millimeters in diameter which show little or no tendency to ulcerate. These are probably embolic in origin.

Amyloid degeneration and chronic nephritis are frequently associated with the tuberculous changes.

In the ureter and renal pelvis the disease manifests itself in three distinct forms: (1) the granular; (2) the superficial ulcerative; and (3) the massive infiltrative which involves the deeper layers. Total obliteration of the ureter is not produced, as might be expected, by deep ulceration with extensive loss of tissue, but results from superficial ulcers which destroy the mucosa and submucosa leaving intact the muscle wall, the occlusion being effected through regenerative changes with scar tissue formation. The periureteral changes are interesting and exceedingly important, too, from an operative standpoint, but we cannot enter into a detailed discussion of them here.

Again, in the bladder three distinct stages of the disease can be recognized and differentiated. (1) The first stage is one of granulation and superficial ulceration involving only the mucosa and submucosa. (2) The second presents deep ulcerations which involve the muscle layers. (3) The third is that of complete destruction of practically the entire thickness of the bladder wall through coalescence and extension of the ulcers. In many cases all three stages coexist, and the bladder wall may vary in thickness from a couple of millimeters to two or more centimeters at different portions. In nearly all of these cases the viscus is markedly contracted, and in some instances the whole bladder may be no larger than a hen's egg.

Thus we find a certain degree of uniformity in the manifestations of this disease in all parts of the urinary tract—whether it be kidney parenchyma, renal pelvis, ureter or bladder. Before dismissing the pathology let me emphasize several points: (1) that the disease in its early stages is a localized process, originating in the kidney through blood-borne infection from some other focus in the body; (2) that certainly in considerably over ninety per cent of the cases it begins as a unilateral disease; and (3) that advanced bladder tuberculosis without involvement of one or both kidneys is rarely, if ever, seen in women; whereas extensive renal destruction with only slight invasion of the ureter and bladder is not at all uncommon.

Now, then, what should lead us to suspect the existence of this disease and how are we to establish the diagnosis? Fortunately, there is rarely any great difficulty, if we are careful to obtain a complete and accurate history, and then resort to the various methods of examination now at our command.

In the first place there are certain facts empirically established that are well worth remembering. The disease is pre-eminently one of young adult life, and is by far the most frequent of all purulent renal affections of this period. It is surprisingly infrequent in phthisical patients, occurring much oftener in apparently healthy individuals springing from healthy families. Not only is it unilateral at the outset in over ninety per cent of the cases, but the relatively infrequent and extraordinarily late involvement of the second kidney is a striking characteristic that obviously has a most important bearing upon the treatment.

The disease may long remain symptomless and be observed first through a mixed infection. On the other hand, while still confined to one kidney and in the early stages it may at any time give rise to any one or all of a characteristic group of symptoms which should lead to its prompt detection. These may be conveniently divided into (a) local, and (b) constitutional symptoms.

#### (a) Local symptoms:

1. *Polyuria*.—This is a constant early symptom and is usually quite marked. It does not continue, however, after the disease has advanced sufficiently to cause extensive destruction of renal tissue.

2. *Frequent and painful micturition*, present both day and night. Also an early symptom which often occurs without any involvement whatever of the ureter or bladder, but is associated especially with cases in which the disease has extended to the renal pelvis. The pain is referred along the course of the ureter and to the neck of the bladder, coming on at the end of urination.

3. *Hæmaturia*.—Intermittent hæmaturia without obvious cause should always be suggestive of renal tuberculosis. It is surprising how many cases exhibit this as the first symptom. The amount of blood is not large as a rule, in fact, it may be only microscopic, but it occurs continuously night and day for days and even weeks at a time, thus differing from the hæmaturia associated with calculus. This usually indicates ulceration of the renal pelvis or papillæ.

4. *Pyuria*.—Present in all cases at some time. The urine is pale, usually acid, but may become alkaline through a mixed infection with pyonephrosis, low specific gravity, and generally contains albumin in amounts proportionate to the extent of the renal changes and the amount of pus present. Do not, however, fall into the common error of excluding renal tuberculosis because of the absence of albuminuria. The two are not invariably associated as is commonly believed. Rovsing has emphasized this point within a few weeks, reporting seven cases in which this sign was entirely absent. The bladder urine contains much more pus as a rule than urine obtained direct from the kidney through a renal catheter or endoscope. The leucocytes found may or may not show degenerative changes. Mononuclear cells



usually predominate, but seventy-five to eighty per cent of polymorphonuclears is not uncommon. The contents of the urine from each kidney vary considerably at different stages of the disease, as one would expect. Remember that a persistent acid pyuria from the sediment of which no organism grows on ordinary media demands that a diligent search be made for renal tuberculosis. Indeed, it is safe to say that we shall not often err, if we assume that we are dealing with renal tuberculosis whenever we find a few leucocytes in the urine of a patient with bladder symptoms, provided the ordinary bacteriologic examination of the urine is negative.

5. *Pain* in the lumbar region over the kidney is not uncommon. It is dull and aching in character and may radiate along the ureter. It may be colicky in type, too, becoming extremely severe when the ureter is blocked by a blood-clot or mass of caseous material thrown off from the disintegrating kidney.

6. When palpable the diseased organ is usually *sensitive*. It may be normal or irregular in shape, but generally is not much enlarged, unless there is an associated pyonephrosis, when it may attain enormous size. Bear in mind, however, that the large, easily felt kidney may be the normal one that has undergone compensatory hypertrophy to meet the extra demands put upon it, whereas the diseased one may be represented by a shriveled sac of inspissated pus tucked deeply away beneath the ribs.

7. *Tubercle bacilli* can be demonstrated in the urine in fully eighty per cent of the cases if persistent and repeated search is made from the twenty-four hour specimens. The proper way to search for them is to examine a couple of slides prepared each day from fresh twenty-four hour specimens, instead of a number of slides from one specimen. Preliminary renal massage with induced diuresis may cause a shower of them to appear in the urine, and is a point worth bearing in mind. Positive animal inoculation is often helpful. It demonstrates conclusively the presence of tubercle bacilli in the urine; but remember that these may be present simply as a product of renal excretion when the entire urinary tract is absolutely free from the disease; so that a single demonstration is of itself not conclusive proof of urinary tuberculosis.

(b) Constitutional symptoms, the most important are:

1. Irregular fever with evening exacerbation. Blocking of the ureter is accompanied by a sharp rise in temperature which continues for several days, probably due in part, at least, to absorption of toxins from the renal pelvis.

2. *Night sweats* are not uncommon in this as in other forms of tuberculosis.

3. *Emaciation* which is often progressive.

When the disease invades the bladder its presence is very promptly heralded by symptoms of cystitis. There is frequent urgent urination day and night, associated with great pain both during and especially at the end of the act. Emptying the bladder affords little or no relief, and as the disease advances a stage is finally reached where marked strangury and tenesmus dominate the symptom-complex. The viscus becomes extremely intolerant and irritable; it robs the unfortu-

nate victim of all restful sleep, causing constant distress, and often, indeed, most excruciating pain. These symptoms, however, may be out of all proportion to the extent and degree of bladder involvement.

*Cystoscopy* is an invaluable aid in enabling us to determine accurately certain important points: (1) to make a positive diagnosis; (2) to determine the extent, location, and degree of bladder and ureteral involvement; and (3) to investigate the functional activity of one or both kidneys. In the advanced cases the bladder is so intolerant of instrumentation as a rule that this examination cannot be satisfactorily conducted without general anaesthesia; but in the early stages—where it is of greatest value—no difficulty whatever is usually encountered. The necessity of general anaesthesia, however, is in itself not a contraindication to the cystoscopic examination being made, but, on the contrary, should be employed whenever necessary.

Generally speaking the bladder does not present a specific picture in the late stages of the disease; the tuberculous nature of the ulcers being conclusively evident only when their relationship to tubercles can be determined, and these are not very commonly found. When observed they appear either discrete or grouped, particularly about the trigonum and ureteral orifices, as minute, slightly elevated, grayish-yellow nodules surrounded by a zone of hyperemia. They are to some extent simulated in appearance by little nodular granulations and minute pearly vesicles filled with grumous material which are quite commonly observed in a variety of bladder conditions; but close examination will always disclose that these lack the characteristic areolar redness, and usually are indiscriminately scattered over the bladder walls. There may be a diffuse reddening and oedema of the bladder lining, or such localized areas may be separated by patches of healthy looking mucosa. Mixed bladder infections are not uncommon in women, producing an acute diffuse cystitis which causes the walls of the viscus to be covered with mucus, pus, or incrustations that quite obscure the associated tuberculosis. Such conditions readily clear up, however, under ordinary treatment with irrigations, etc., which, on the contrary, serve only to aggravate tuberculous cystitis. Of distinct diagnostic value is the fact that tuberculous ulcers are not widespread in the bladder as a rule, but tend to localize about the trigonum and ureteral orifices. They present an irregular outline with elevated, thickened, undermined edges surrounding an unhealthy base which is covered with dirty, necrotic material. A zone of dense infiltration is constantly observed around them. One characteristic is the absence of incrustations or phosphatic deposits so commonly found on non-tuberculous ulcers. If the bladder is examined while the disease is still confined to the region of one ureteral orifice, pictures are seen which may be considered practically diagnostic. Thus ulceration confined to this region indicates that the kidney of that side is almost surely tuberculous. A puffy, red ureteral orifice in an otherwise healthy looking bladder is very suggestive. So also is the retracted, crater-like ostium. Sometimes the orifice is found enclosed in a circle of little vesicles of uniform size and symmetrically arranged—the so-called bullous oedema—which is considered pathog-

nomonic of descending renal tuberculosis. As the ulceration and infiltration advance the ureteral orifices are distorted into a variety of shapes, becoming irregular in outline and often gaping widely. Occasionally the diseased ureter is visible for two centimeters as an elevated cord obliquely traversing the wall of the viscus.

Accumulated experience seems to justify catheterization of a sound ureter through a tuberculous bladder in cases of unilateral infection, for the purpose of investigating the competency of the non-tuberculous kidney. Many of the world's most conspicuous leaders in this field who have consistently practised this procedure for years in large numbers of cases state explicitly that they have never seen ascending renal infection follow it. Experimental work has shown that it is exceedingly difficult to produce ascending renal tuberculosis by the simple introduction of tubercle bacilli into the lower end of a healthy ureter. Moreover, even in cases of bladder tuberculosis sufficiently extensive to interfere through ulceration and infiltration with the mechanism which normally closes and safeguards the ureteral orifice, so that during vesical contraction the ostium gapes widely and permits reflux of infected urine, ascending renal infection is the exception rather than the rule. In an extensive search through the literature I have been unable to find any statistics showing the relative frequency of occurrence of the disease in the remaining sound kidney of patients who had the healthy ureter catheterized at the time of operation, as compared with those in whom ureteral catheterization was omitted. But the unanimity of opinion among those most competent to speak upon this point makes it reasonably certain that the danger of infecting the healthy side is negligible, either with the direct or indirect method of cystoscopy, provided one employs certain simple precautions. These are thorough preliminary irrigation of the bladder, induction of active diuresis, administration of urinary antiseptics, and the careful introduction of the catheter a distance of only two or three centimeters up the ureter with a minimal amount of trauma.

Certainly the danger is far outweighed by the importance of determining as accurately as possible the functional capacity of the supposedly sound kidney before removing one known to be tuberculous. It is not within the scope of this paper to discuss the relative merits of the various methods at our disposal for doing this. In women the problem is greatly simplified through the use of the Kelly cystoscope with air distention of the bladder. With this simple instrument we are able to get a pretty accurate idea of the condition of the presumably healthy side without introducing a catheter into the ureter at all. Valuable information may be obtained in several ways. Thus with the patient in the knee-chest posture and the bladder fully distended with air, by simply placing the end of the cystoscope directly over the ureteral orifice so that the urine spurts into the tube, within a few minutes we can collect sufficient urine for chemical, bacteriologic and microscopic study. So, too, we can observe directly the exact time of appearance in the urine of the anilin dyes, such as methylene-blue or indigo-carmin, that have been given hypodermically. Of

still more value is the method of obturating the ureter of the diseased side with a large flute-end catheter, so that no urine flows into the bladder from this side, and then, after washing out the bladder, to collect the urine from the healthy side transvesically. This is not reliable for bacteriologic study, but is an excellent and satisfactory method of applying the various functional tests to this class of cases. Moreover, an experienced observer who knows how to make due allowance for bladder contamination learns much of practical value from the gross appearance as well as the microscopic and chemical study of specimens thus obtained. If circumstances seem to justify the introduction of a catheter into the healthy ureter, it can be most safely done through the open cystoscope which permits one to cleanse and partially disinfect the ureteral orifice in addition to the precautionary measures already enumerated before the catheter is inserted. This comparative study by volumetric, colorimetric, bacteriologic, chemic and microscopic methods of the urine collected separately from the two sides is of the greatest help in establishing the diagnosis, revealing the extent of the disease and determining the competency of the non-infected kidney.

It becomes evident from what has been said that the diagnosis of urinary tuberculosis in women should not be a difficult matter. To summarize a careful history will often bring out protracted exposure to tuberculous infection followed in time by some or all of the symptoms enumerated above. Renal tuberculosis is the most frequent of all suppurative diseases of the kidney from twenty to forty years of age. Unexplained cystitis, even of a mild grade, in a young person should of itself excite suspicion of tuberculosis, because in other forms—such as gonorrhœal, that due to the colon bacillus or other common organisms, or associated with tumors, calculus, foreign bodies, stricture of the urethra, cystocele, etc.—the cause is readily demonstrable; thus the insidious onset becomes of distinct diagnostic value. The general physical examination will not infrequently disclose a primary focus elsewhere in the body. Locally one finds in many cases a sensitive kidney; a sensitive ureter on abdominal palpation just over the point where it crosses the pelvic brim; on vaginal examination the thickened, beaded ureter easily identified traversing the anterolateral fornix; and the infiltrated, hypersensitive trigonum. The bladder capacity is greatly reduced—a contracted, irritable viscus, intolerant of any instrumentation. The cystitis is of a type that resists or may even be aggravated by treatment with irrigations, especially if silver salts—so valuable in other bladder infections—are used. Then a persistent acid pyuria is present from which no organism grows on ordinary media and is associated with the other urinary characteristics already described, including the demonstration of the tubercle bacillus. The cystoscopic findings and the comparative functional tests furnish indispensable information, as detailed above. Further, the radiographic disclosures may prove of great assistance, especially when intensified by the preliminary introduction into the renal pelvis of some substance impervious to the rays, such as collargol. And finally, one may profitably resort to the use of tuberculin as a diagnostic measure in properly

selected cases. If after exhausting all these measures the surgeon is still uncertain as to the competency of the supposedly healthy kidney, it is a perfectly legitimate procedure to investigate it directly and thoroughly through an exploratory lumbar incision before removing its diseased fellow. This course, indeed, has been enthusiastically recommended by some surgeons in all cases where nephrectomy is to be undertaken for any reason whatever.

The treatment of the disease has already been indicated. No matter at what stage it is discovered, nor how extensive the bladder involvement, but provided only it is unilateral so far as the kidneys are concerned, nephrectomy—nephroureterectomy, if the ureter is extensively diseased—should be promptly performed. If but one kidney is slightly involved while the other is practically destroyed or converted into a pus sac, the latter should still be removed or first drained and later removed, and the patient's health will generally be benefited as a result. If there is still some secretory tissue left in the worse damaged kidney of a patient afflicted with advanced bilateral disease, nephrostomy with establishment of a permanent lumbar fistula, is a useful palliative measure. In determining the treatment of a specific case remember that the associated albuminuria so commonly found on the non-tuberculous side generally disappears after removal of the infected kidney. This is probably a toxic or perhaps a true reflex albuminuria. I am convinced that it is a dangerous thing to temporize in the early cases by treating them with tuberculin alone, or in conjunction with other therapeutic, hygienic and climatic measures in an effort to avoid operation. How, as a matter of fact, are we to determine which are the early cases? Surely it has been amply shown that the severity of the symptoms is not a reliable criterion. Besides, spontaneous healing of renal tuberculosis has not been satisfactorily demonstrated, so far as I know; unless the apparent healing following extensive destruction of the organ with its conversion into a sterile pyonephrosis or sclerotic kidney be so regarded. On the other hand, there is no scarcity in the literature of cases coming to operation or autopsy after weeks and months of treatment with tuberculin, but in every instance that has come to my notice not only was there complete absence of any attempt at healing in the kidney, but fresh foci of the disease were repeatedly encountered. The advocates of conservative management of the incipient cases have not been able, therefore, to produce convincing proof in support of their claims, and consequently some of the most ardent of them have become deserters within the past few years and have come over to join the ranks of the majority who believe in early and radical operation, and whose results certainly seem to leave no doubt as to the wisdom of this course. After removal of the diseased kidney in cases of unilateral infection the bladder involvement, even though extensive, will heal spontaneously in nearly all cases. This may be hastened by appropriate treatment. If only a single focus exists in the bladder, or if there are multiple discrete ulcers, it is helpful to apply the actual cautery or strong silver nitrate. It is still better to excise the ulcerated area when possible. If the disease is too extensive to be successfully treated by these

methods, instillations of a iodoform—olive-oil emulsion, or of carbolic acid, or of bichloride of mercury are of distinct value. The last named is probably the best; beginning with weak solutions and small amounts and gradually increasing until 50 cc. of a 1:10,000 or 1:5000 strength can be retained. These should be given twice a week, and the bladder should not be distended. Carbolic acid, too, is highly recommended. It should be used as advocated by Rovsing, who after washing out the bladder, introduces 50 cc. of a six per cent solution, which is left for three to four minutes and then removed. This is repeated until the solution returns clear. At first the instillations are given at intervals of two days, then at longer intervals of one, two, and three weeks or a month. Both the bichloride and carbolic instillations are exceedingly painful and morphine should be freely used when they are given. It is important also to allay the constant pain during the intervals between treatments so that the patient may secure restful sleep; for this purpose opium and belladonna in the form of suppositories is the best medication. The usual hygienic and dietetic measures adaptable to tuberculous cases in general should also be systematically employed in patients suffering from urinary tuberculosis, whether operated upon or not. Aside from tonics and sedatives, internal medication is of very little value; such urinary antiseptics as urotropin, salol, salicylic acid, oil of sandal-wood, etc., failing utterly, unless there is a mixed infection. Casper says that the only rational internal remedies are creosote, guaiacol carbonate and ichthyol, either of which he allows without restriction as long as the patient can tolerate them. He recommends that these drugs be given in oil enemata, because they are so unpalatable— $\frac{3i}{5}$  to  $\frac{3vii}{5}$  of olive oil and inject a small syringe-ful into the rectum twice daily. Mineral waters are useful for diluting the urine and thus rendering it less irritating. In cases of bilateral disease, in inoperable cases, and as a post-operative measure in advanced bladder tuberculosis, tuberculin should certainly be given a cautious trial therapeutically. The general condition of the patient is said generally to improve following its use, due, Wildbolz thinks, to its fortifying the organism against the toxins of the bacilli rather than to stimulating local healing processes. In the hopeless cases with intolerable pain, permanent vesical fistula, or complete deflection of the urine from the bladder by dividing the ureters and bringing their proximal ends out to drain permanently through lumbar incisions are most grateful palliative measures.

Pregnancy quite certainly aggravates renal tuberculosis. Generally speaking, if the disease is unilateral, nephrectomy should be done and the pregnancy be allowed to go on undisturbed, but bilateral involvement is an indication for abortion.

In conclusion, I wish to report briefly a case that demonstrates very forcibly how insidious and deceptive this disease may be, and how important it is never to remove a tuberculous kidney until the condition of the supposedly healthy one has been accurately determined.

A few months ago, Mrs. J. E., white, age twenty-nine years, was referred to me by her family physician on account of obstinate symptoms of cystitis. The history pointed strongly to tuberculous



involvement of the left urinary tract and bladder, but did not cast the slightest suspicion upon the right side. The left kidney was not palpable, but there was marked sensitiveness and muscle rigidity along the course of the left ureter, the lower portion of which on vaginal examination was felt to be greatly thickened, nodular and exquisitely painful to touch. On the right side, however, palpation revealed no abnormality whatever, either with reference to the kidney or ureter. On cystoscopic examination the left ureteral orifice presented the unmistakable picture of tuberculosis; it was retracted and surrounded by the typical bullous oedema, and areolar redness already described, whereas the remainder of the bladder, including the right ureteral orifice, presented no noteworthy abnormality. Purulent urine was observed spurting from the left orifice at regular intervals, but although the right orifice was carefully watched for some minutes, it was not seen to functionate at all. This first aroused my suspicions with reference to the right kidney, and I again questioned the patient closely, but could not obtain any evidence of its ever having caused the slightest symptom. Two days later, after induced diuresis, I repeated the cystoscopic examination and again observed the right ureteral orifice almost continuously for twenty minutes or more, but again failed to see any urine expelled. After an interval of a few days still a third attempt was made to get some idea of the functional capacity of the right kidney, but with the same negative result as before. Instead, therefore, of carrying out my original intention of doing a left nephroureterectomy, I decided to first explore the right

kidney and determine its condition. After exposing it through a lumbar incision I found that it had been almost completely destroyed and converted into a pus sac, the thin wall of which contained only a vestige of renal tissue left. This condition had been brought about by a tuberculous stricture of the ureter situated just at its origin from the renal pelvis, which had given rise to a pyonephrosis, and this in turn was responsible for the extensive destruction of renal parenchyma. The organ was a little larger than normal, but its general contour was not much changed, and below the point of stricture the ureter was perfectly healthy.

It is remarkable that such extensive destruction could have occurred without ever having produced a single symptom referable to this side. The case illustrates very forcibly, therefore, how insidious this disease may be and how imperative it is to explore the supposedly healthy kidney whenever its condition cannot be satisfactorily determined in any other way, before removing its fellow known to be tuberculous. Had the single clue pointing to the right side in this case not been followed, notwithstanding the fact that its involvement was contradicted by all the clinical evidence, and had the left kidney been removed as was originally planned, prompt fatality would, of course, have been the inevitable result.

## THE EFFECT OF CHEMICAL TREATMENT UPON THE BALTIMORE CITY WATER.

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In previous papers<sup>1</sup> we have pointed out the extreme pollution of the Baltimore City water supply and have described some of the organisms which may be isolated from it. This water practically always has contained an excessive number of bacteria, the count fluctuating between twenty-five hundred and five thousand per cubic centimeter. This high bacterial content is not of itself dangerous nor to be wondered at when we consider the broad area of rather thickly settled farming land which makes up the watershed of the Gunpowder River, our chief source of supply. The dangerous feature of our water is the predominance of bacteria evidently derived from the intestinal tract of man and animals, fermenting organisms occurring with great regularity in one cubic centimeter quantities and not infrequently in dilutions of 1-10 and 1-100. Plates poured from these fermentation tubes reveal *B. coli* as the usual fermenter, but we frequently find organisms belonging to the "cloacæ" group. A species closely related to *B. cloacæ* of Jordan has also been isolated on a number of occasions and we have been particularly interested in its study. This organism resembles *B. coli* in many of its cultural features, having the same gas formula, a predominance of hydrogen over carbon dioxide. It is, however, a rapid liquefier of gelatin, the liquefaction taking place within three or four days. It is evidently the organism which at various times has been designated as a "liquefying colon." Agar and gelatin plates from the water also show colonies characteristic of intestinal bacteria and not the pigmented and spore-bearing organisms found normally. These colonies are usually *B. coli*

or some other fermenter, but *B. faecalis alkaligenes* of Petruschky is quite a frequent isolation.

During most of the time at which the water has been studied qualitatively with a view to discovering the kinds of organisms encountered in it the various species have exhibited a somewhat constant ratio to each other, *B. coli* being the most frequent fermenting organism, the others appearing much more rarely. In the summer of 1910, however, at the time of a severe drought in Baltimore and Maryland, the number of liquefying fermenting organisms was greatly increased at the expense of *B. coli*.<sup>2</sup> At this time the presumptive test was positive constantly in a dilution of 1-100 and on one occasion in a dilution of 1-1000. Plates poured from these fermentation tubes revealed few colonies of *B. coli*, but a variety of organisms belonging to the "cloacæ" group. During this period the bacterial count was not above what may be regarded as normal for the Baltimore water approximating four to five thousand per cubic centimeter. This increase of pollution or concentration of the sewage in the water was coincident with the summer rise of typhoid fever, Baltimore being in the grip of a fearful epidemic of the disease in 1910. The number of reported cases of typhoid fever for the year reached nearly 1900 (1890) with 235 deaths in a population of 585,000. By far the larger number of these cases and the highest mortality from the infection occurred during the extremely hot, dry weather of August, September and October, the case incidence and the morbidity not falling to normal until the end of December. While a definite causal relation between the con-

tamination of the city water and the enteric fever could not be made out, the variations from month to month in the amount of typhoid when compared with the rise and fall of the pollution of the water supply were extremely suggestive as indicating such a relation.

In June, 1911, the city officials of Baltimore, under the direction of Dr. Stokes,\* city bacteriologist, began the treatment of our water supply with calcium hypochlorite. This was added to the impounding reservoir of the Gunpowder River in amounts varying from 0.4 of 1 part of available chlorine per million parts of water to 1.5 parts per million. Since that time the treatment has been continued up to the present, but in June, 1912, at the suggestion of Dr. Stokes, alum was also added to the water. Beginning a few months after the hypochlorite treatment was instituted we were able to make weekly examinations of the Gunpowder water over a period of

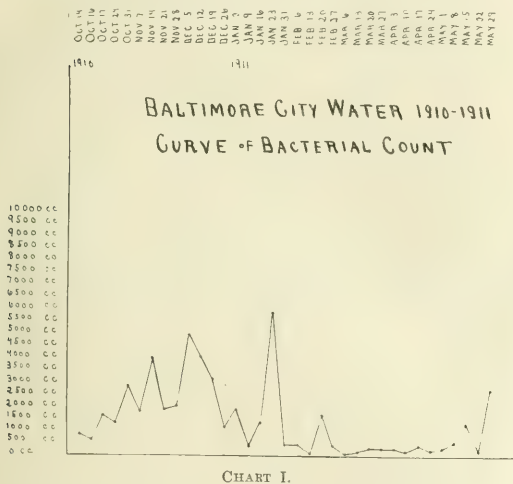


CHART I.

thirteen months, Dr. Mary R. Fleming conducting these experiments during the summer season. We were particularly anxious to determine the effect of the chemicals upon the microorganisms present in the water by comparing bacterial counts over fairly long periods before and after the treatment. In a recent paper Stokes (*l. c.*) has called attention to the percentage decrease in organisms following the addition of the hypochlorite, taking his samples from the Gunpowder River before treatment and from the city taps, the bacterial reduction varying from 89 to 97 per cent. Our own method of examination differs somewhat from that of Stokes, but brings out the same point. By comparing Chart I, which gives the bacterial content of the water during 1910 and 1911, with Chart II, for 1911 and 1912, it may be seen that the bacterial content was the same and that fluctuations of about the same character were present during both periods up to July, 1912. From this time on the number of organisms has been persistently and definitely lower. Over a period of four months the city water showed less than 500 bacteria per cubic centi-

meter, a condition not heretofore encountered in our studies. But one similar period has ever been observed, in March and April, 1911. This lasted but a short time, however. The 1912 period of low bacterial content is coincident with the period when both alum and hypochlorite had been added to the water. It would seem therefore that the treatment with hypochlorite alone did not have a marked influence upon the character of the Baltimore City water, but that a definite diminution in the number of organisms appeared when the alum treatment was utilized as well as the hypochlorite.

When we come now to the consideration of the presence of fermenting organisms a remarkable condition presents itself. These organisms have been but little affected if at all by the addition of chemicals. If we compare the various quantities of water required to give positive presumptive tests during the past thirteen months (Chart III) excepting a short time in 1910

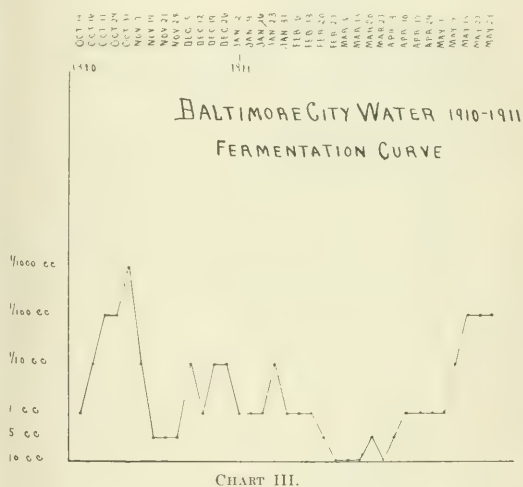


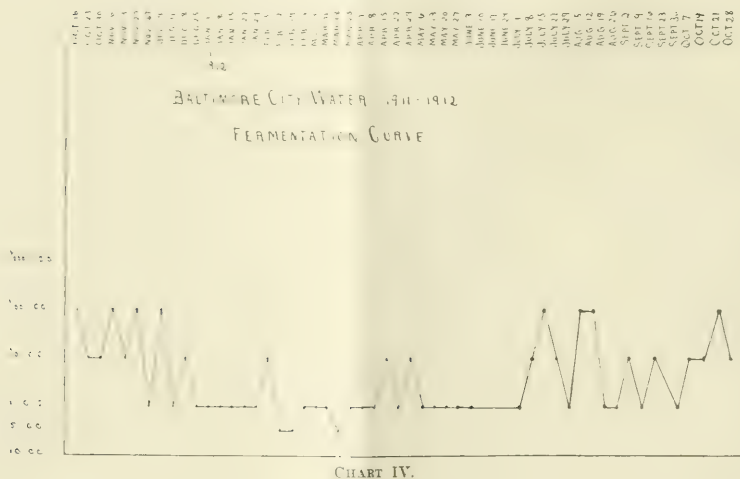
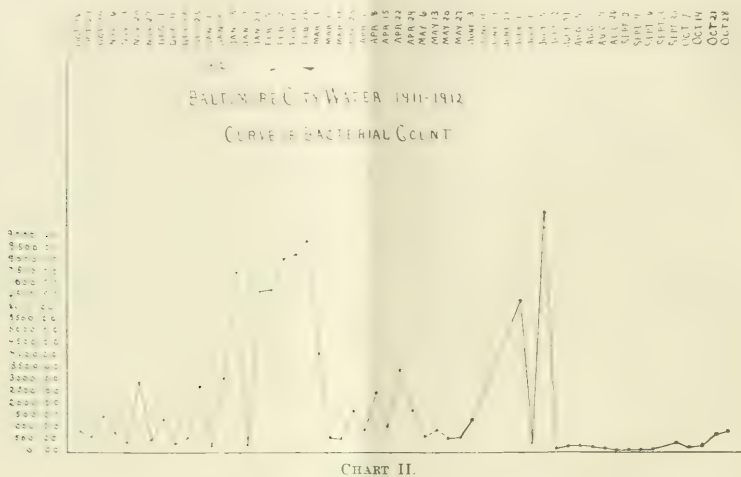
CHART III.

when the degree of pollution was extreme, with the quantities required before this period (Chart IV), little or no difference can be noted. During almost the entire time, both before and after the treatment, the presumptive test has been positive in quantities of 1 cubic centimeter, 1-10 and 1-100 of a cubic centimeter. Even during the period of low bacterial count, in the summer of 1912, fermentation occurred with great regularity in a dilution of 1-10. The organisms have also in our experience remained the same qualitatively, *B. coli* being the predominant form with the occasional appearance of liquefying fermenters. These results are somewhat at variance with results obtained elsewhere. In general coincident with the drop in the bacterial count after chemical treatment, a drop in the number of fermenters can also be made out. It is evident that the Gunpowder water offers some special resistance to the action of calcium hypochlorite alone and to this chemical in combination with alum. Possibly, as Stokes has suggested, a different method of applying the treatment, as by adding the chemicals to the water after sedimentation in the storage

reservoirs, is necessary in order to obtain a complete elimination of the intestinal bacteria from the supply. It is also possible that the continued high bacterial counts which we have found are the result of after growths of spore-bearing bacteria. Our plates have not, however, indicated this to be the case.

instituted in June, 1911, and it apparently kept the typhoid fever down during the subsequent summer season and during the season just past without, however, eliminating the summer rise.

Just how much typhoid fever in Baltimore is water-borne



Finally the question rises as to what effect the chemical treatment of the water may have had upon the typhoid fever in Baltimore and particularly upon its summer rise. This is a question of great complexity and one in which there is room for abundant discussion. As Stokes (*l. c.*) has pointed out, there has been a steady diminution in the amount of our typhoid fever since the year 1910. This is well brought out in Charts V and VI which give the case incidence and mortality for the past six years. The chemical treatment was

in origin is of course an open question. Certainly a considerable part of the disease here can with reasonable certainty be ascribed to contamination of the supply, since cases of typhoid fever upon the water shed are by no means infrequent. The chemical treatment has probably had a pretty definite influence in cutting down the typhoid due to this factor and the steady diminution of the disease in 1911 and 1912 can reasonably be ascribed to it. That the summer rise has not been eliminated, but merely diminished in intensity, cannot be regarded as an



argument against the value of the method. The conditions in Baltimore are extremely complicated, just as they are in other cities in America with a large colored population, a hot summer climate and a poorly controlled milk supply. The typhoid

summer. The results already obtained, however, are so favorable, despite the resistance of the water to chemical treatment and despite the continued presence of typhoid fever in our midst, as to justify the use of chemicals in our water supply

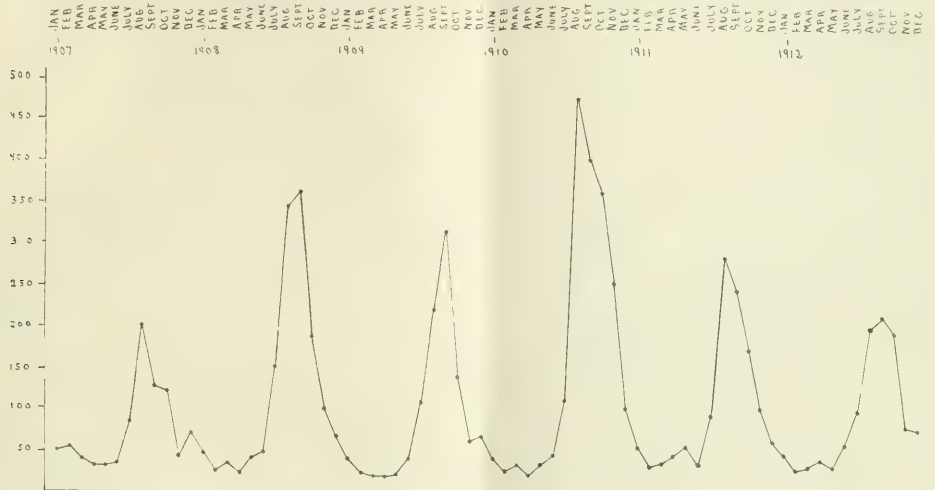


CHART V.—Typhoid Fever Case Incidence, 1907-1913.

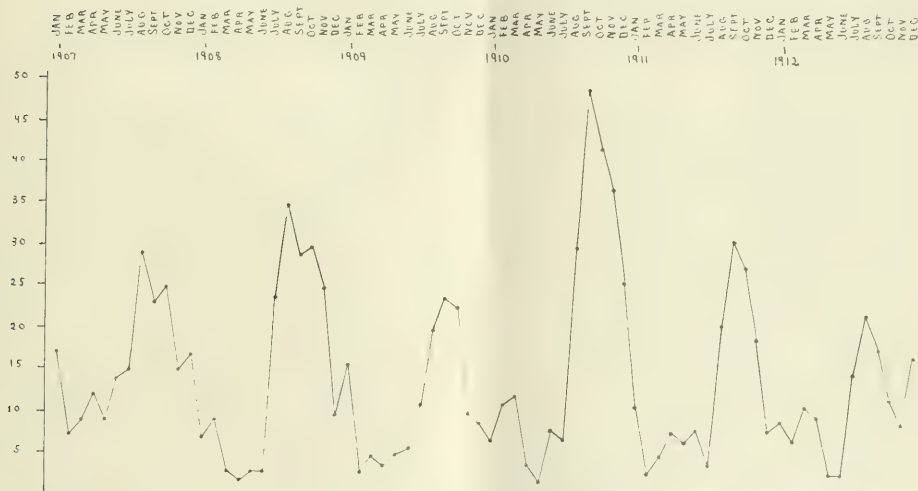


CHART VI.—Typhoid Fever Mortality, 1907-1913.

fever from direct contact, from milk, from bacillus carriers will not be influenced to any marked extent by water purification, except as any diminution of the disease from one factor is bound to cause diminution of the disease from other factors by cutting off the sources of infection. Further experience alone can determine whether the fall in typhoid already noted will continue. The water is constantly improving in character and more marked results may be looked for during the coming

until a filtration plant is built and established upon a satisfactory working basis.

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# CERTAIN DANGERS OF THE ADENOID OPERATION.\*

By W. E. GROVE, M. D., Milwaukee, Wis.

The adenoid operation is the most frequent operative procedure of the rhinologist, laryngologist or otologist. This operation is regarded by the laity and by a great many physicians as quite simple and absolutely harmless, and, if we consider the large number of these operations performed every year, and the relatively meagre statistics of its complications, it does not surprise us that this opinion is prevalent. There are three reasons for the meagreness of statistical material concerning this operation. First, few surgeons enjoy publishing their accidents. Second, the operation is generally performed outside of a hospital and the surgeon does not usually control his patient long enough after the operation. Third, the operation is frequently performed by the general physician who is too busy to publish his results.

The most frequent and dangerous complications of the adenoid operation can be placed in two general groups: 1, post-operative bleeding; 2, post-operative infections. The post-operative bleeding can be of a very severe nature. This can be seen from the work of Barrell and Orr<sup>1</sup> who, in 1907, reported 7 cases of fatal bleeding after the adenoid operation; also from the work of Heymann<sup>2</sup> in which Burger is reported to have collected from the literature 40 cases of severe bleeding, with 3 or 4 deaths.

I have prepared this paper under the stimulus of two post-operative infections and in the hope of being able to throw a little light on the second large group of the *infectious complications of the adenoid operation*.

That such post-operative complications must occur is apparent when we remember that the operation is done by sense of touch and in an already infected field which cannot be surgically cleaned. Indeed, the fever which usually appears after most adenoid operations is an indication of an infection which the organism is in most cases able to overcome.

The bacteriological flora of the nose has been described by Kobrak,<sup>3</sup> Brieger,<sup>4</sup> Delsaux,<sup>5</sup> Burack,<sup>6</sup> Walter<sup>7</sup> and Winkler.<sup>8</sup> Brieger frequently found large numbers of microorganisms on the surface of adenoids in children in whom the mechanical cleansing of the nose was hindered by a deficient power of forceful expiration. If, after carefully cleansing the vestibulum, the nose was now blown upon plates or into bouillon he found numerous colonies of various organisms; i. e., streptococci, staphylococci, diplococci and bacteria of various sorts. In order to prove that a certain number of these organisms

came from the surface of the pharyngeal tonsil, he carefully placed coloring matter on the surface of the adenoids, which coloring matter was soon after found in the nasal excretions. Walter (*l. c.*) found staphylococci present in 56 of 100 cases, which he examined for acute or subacute rhinitis, and according to Haslauer,<sup>9</sup> these organisms are present in 25 per cent of all normal noses. Walter also found other organisms present, among which were the *B. segmentosus* of Cautley, the *micrococcus catarrhalis*, the *B. mucosus capsulatus* and the pneumococcus. It is also a well-known fact that the diphtheria bacillus is frequently present in the tonsillar crypts of the chronic bacillus carriers.

It is a very well-known fact that these microorganisms are either non-virulent or of a low grade of virulency. Brieger (*l. c.*) is of the opinion that the virulency of these organisms is increased after operation, due to the fact that the bactericidal fluids of the tonsil, which usually flow toward its external surface and exert there a bactericidal inhibition, are removed by the excision of the adenoid tissue.

Kobrak (*l. c.*), on the other hand, who examined the relative numbers and virulence of the microorganisms present before and after operation, found, in contradistinction to Brieger, that the number and virulence of these bacteria were only increased in such cases where there was a preexisting nasal or aural infection.

The fact that trauma itself can call forth inflammation is a well-recognized one in pathology. Kobrak believes that it is much more sensible to hold the trauma as the chief inciting agent for the infection, especially in such a field as the nasopharynx, where a latent infection is practically always present. This must be particularly true in the chronic carriers of the diphtheria bacillus and the meningococcus. Burack (*l. c.*) is also of the opinion that the post-operative infection is due to the fact that the virulence of bacteria already present is increased through the trauma of the operation or the loss of blood.

Fever has been very frequently observed after adenoid excision. Kobrak records 30 out of 100 cases with fever, whose average duration was 3.3 days, and whose height did not in any case exceed 102.2° F. Microscopic examination of the adenoid tissue in these cases did not show them to be infected.

Winkler,<sup>10</sup> who always operates in a hospital, reported temperature in 50 per cent of 58 cases. Burack (*l. c.*) found a temperature in 58 out of 540 hospital operations. All these observations point to the fact that infectious processes do occur after adenoid excision. That they do not more frequently lead to more serious complications is best explained, to my mind, by the fact that the *operative field presents a broad surface with excellent free drainage*.

Generalized septicemias are not unknown after the adenoid

\* Most of the material for this paper was collected in the University Klinik of Prof. Gerber for Diseases of the Nose and Throat at Koenigsberg, Germany.

<sup>1</sup> Barrell and Orr: Zentralbl. f. Laryngol., xxiii, 163.

<sup>2</sup> Heymann: Arch. f. Laryngol., 1908, p. 15.

<sup>3</sup> Kobrak: Arch. f. Laryngol., xix, 320.

<sup>4</sup> Brieger: *Ibid.*, xii.

<sup>5</sup> Delsaux: Zentralbl. f. Laryngol., iii, 27.

<sup>6</sup> Burack: Zeitschr. f. Laryngol., iii.

<sup>7</sup> Walter: J. Am. M. Ass., 1910.

<sup>8</sup> Winkler: Verhandl. des Vereins suddeutsch. Laryngol., 1906.

<sup>9</sup> Haslauer: Cit. by Walter (*l. c.*).

<sup>10</sup> Winkler: Cit. by Kobrak (*l. c.*).

operation, six such cases having been reported in the literature by Brieger, Shurley,<sup>11</sup> Schramm<sup>12</sup> and Parrel.<sup>13</sup>

Coley<sup>14</sup> from his own practice described one case of endocarditis after adenoid removal and reported two other cases from the literature. A patient of Montengohl<sup>15</sup> was taken with an attack of chorea and endocarditis after an adenoid operation. In a paper by Delsaux (*l. c.*) Broeckart is cited as having seen a post-operative case of combined endocarditis and acute articular rheumatism. Bernhard<sup>16</sup> also reported one case of acute articular rheumatism as a complication of the adenoid operation.

Practically all of the acute infectious diseases of childhood have been observed as post-operative sequelæ. In his paper on the complications of the adenoid operation Delsaux (*l. c.*) reports one case of a rubeola-like eruption, four cases of scarlatiniform erythema, and Brieger (*l. c.*) operated during the incubation stage of chicken pox and observed after the operation a full-blown pseudodiphtheritic localization of the chicken pox in the pharynx.

The cases of scarlet fever and diphtheria which have been reported as complications of the operation can be explained in two ways. Either the operation was carried out during the incubation stage of these conditions or it was performed in patients who were chronic bacillus carriers, in whose throats the bacillus of diphtheria or the virus of scarlet fever was present in latent or non-virulent form. All together 8 cases of post-operative scarlet fever are reported by Kobrak, Burack and Bernhard, and 6 cases of diphtheria were reported by Kobrak and Hennebert.<sup>17</sup>

In the above we have described the general infectious complications of the adenoid operation. Acute local post-operative infections are also quite frequent. It is almost to be expected that when one removes one part of Waldeyer's ring that an acute infection of the remaining lymphoid tissue will occasionally be seen. Only the fact that both pharyngeal and faucial tonsils are removed so often together can explain the fact that we do not see these post-operative anginas more frequently than we do. These anginas have been described by Delsaux (*l. c.*) Hicquet<sup>18</sup> and Trofinow.<sup>19</sup> The latter saw 5 cases of post-operative angina follicularis among 508 adenoid operations. Gerber<sup>20</sup> saw a peritonsillar abscess develop a short time after the removal of an adenoid in an adult.

It is well known that the regional lymph glands are at times swollen and sensitive to pressure. Rivière<sup>21</sup> observed one case of adenitis among 150 cases of operated adenoids, and Grönbeck<sup>22</sup> describes 4 cases of extensive post-operative affec-

tion of the cervical lymph glands, which called forth severe and long lasting symptoms. Thost<sup>23</sup> saw, 8 weeks after operation, an abscess of the left lateral pharyngeal wall and a swollen fluctuating gland at the angle of the jaw which discharged a tablespoonful of pus after incision.

I should now like to call attention to a group of complications of the adenoid operation which are not infrequently observed, that is, torticollis or wry neck. I have been able to collect 9 cases of this complication from the literature (Thost *l. c.*, Bjalik,<sup>24</sup> Weinstein,<sup>25</sup> Neufeld,<sup>26</sup> and Jacques,<sup>27</sup> who declared that he had seen this complication frequently). Most operators can remember cases from their own practice where the operated child had, for several days after the operation, a stiff neck and one very painful on movement or manipulation. Most of these accidents make their appearance in the first two to five days after the operation, accompanied by a moderate rise of temperature. In the cases of Thost, Bjalik and Neufeld the cervical glands were found to be very much swollen and sensitive to pressure. Neufeld explains this complication as due to an infection of the deep-lying cervical lymph glands. Hicquet (*l. c.*), however, is of the opinion that this complication is not always of infectious nature, but is in some measure due to the force used in operating and to the extent that the anterior bodies of the vertebrae and their ligaments have been injured. Most of these cases improve in a period ranging from two days to two months. We cannot, however, consider the case of Preobraschenski<sup>28</sup> as of infectious nature, a case in which the torticollis lasted three years. He thinks it not impossible that during the operation a branch of the N. accessorius to the MM. trapezius and sternocleidomastoideus was injured.

Erysipelas after the operation has been reported by Burack (*l. c.*), and Grunnert and Meier,<sup>29</sup> but in the case of the last-mentioned authors the erysipelas was caused by the fact that the patient visited another patient ill with erysipelas immediately after the operation. Herz<sup>30</sup> reports a case of phlegmon of the neck as a complication of adenoid extirpation.

Post-operative lung infections are also recognized. These infections, however, are not directly dependent upon post-operative infections, but are rather due to the aspiration of blood or lymphoid tissue during the operation. In a case of Brieger's, where he operated after a cautery treatment of the nose and before the complete separation of the eschar, a post-operative pneumonia developed with large numbers of streptococci in the sputum as well as a streptococcic middle ear infection and a mastoiditis. Fallas<sup>31</sup> reports a case in which a lung abscess developed four days after the operation.

Even cases of lethal meningitis have been reported after the

<sup>11</sup> Shurley: Zentralbl. f. Laryngol., xviii, 412.

<sup>12</sup> Schramm: *Ibid.*, xxi, 379.

<sup>13</sup> Parrel: *Ibid.*, xxv, 273.

<sup>14</sup> Coley: *Ibid.*, xxi, 209.

<sup>15</sup> Montengohl: *Ibid.*, xix, 234.

<sup>16</sup> Bernhard: Cited by Kobrak.

<sup>17</sup> Hennebert: Zentralbl. f. Laryngol., xix, 234.

<sup>18</sup> Hicquet: *Ibid.*, xxvii.

<sup>19</sup> Trofinow: Cit. by Nitikin, *ibid.*, xxvii, 210.

<sup>20</sup> Gerber: Personal communication.

<sup>21</sup> Rivière: Zentralbl. f. Laryngol., xvii.

<sup>22</sup> Grönbeck: *Ibid.*, xix.

<sup>23</sup> Thost: (*l. c.*)

<sup>24</sup> Bjalik: Zeitschr. f. Laryngol., iv, 598.

<sup>25</sup> Weinstein: Mediz. Klinik, 1909, No. 19.

<sup>26</sup> Neufeld: Arch. f. Laryngol., xx, 480.

<sup>27</sup> Jacques: Zeitschr. f. Ohrenheilk., xliii.

<sup>28</sup> Preobraschenski: Arch. f. Laryngol., xxiii.

<sup>29</sup> Grunnert and Meier: Arch. f. Ohrenh., xxxviii.

<sup>30</sup> Herz: Zentralbl. f. Laryngol., xix.

<sup>31</sup> Fallas: *Ibid.*, xxv, 23.



so-called simple and non-dangerous adenoid operation. Schönmann<sup>23</sup> and Shurley<sup>24</sup> have each reported a case and Putnam<sup>25</sup> has described two such cases from his own practice. Schönmann, however, does not think that his case can be counted in as one of the complications of the adenoid excision, inasmuch as the first symptoms of the meningitis appeared 14 days after the operation. In the meantime the boy had been attending school.

In the preceding remarks I have taken up the following post-operative complications of the adenoid operation, fever, general sepsis, endocarditis, acute rheumatic fever, the acute infectious diseases of childhood, tonsillitis, adenitis, torticollis, lung infections and meningitis, and have pointed out their causal connection with the bacterial content of the nose and naso-pharynx.

Two systems of accessory mucous membrane lined cavities are in fairly close connection with the naso-pharynx, namely, the pneumatic cavities of the ear and the accessory sinuses of the nose. The pneumatic spaces of the ear are brought into direct connection with the naso-pharynx by means of the Eustachian tube and it is a well recognized fact which needs no further comment or statistics that the ear infections belong to the frequent if not the most frequent of the post-operative complications of the adenoid operation and as such are rightly to be feared.

It is not these ear complications that I wish to consider at this time, but rather the post-operative infections of the other series of pneumatic cavities, the accessory sinuses of the nose. The nasal sinuses, however, from the literature, appear to be much less frequently infected after adenotomy than the ear and its appendages. This may be partly explained by the fact that the operative field lies in much closer approximation to the mouth of the Eustachian tube than to the nasal openings of the accessory sinuses. It may also be explained by the fact that the middle ear, as the result of a partial closure of the Eustachian tube by the pressure of the adenoid, and the consequent damming back of its secretions, is rendered a *locus minoris resistentie*.

In fact, the post-operative infections of the nasal accessory sinuses have received very little attention in the literature. Burack (*l. c.*) states that sinus suppurations after adenotomy have been observed, but does not give any references. Shurley (*l. c.*) also calls attention to the possibility of such infections without pointing to any particular cases.

Henke<sup>26</sup> described the first definite case of sinus suppuration as a complication of the adenoid operation. His case was that of a 13-year-old girl in Gerber's clinic in whom a severe frontal sinus infection with periostitis, edema of the eyelids and neighboring soft parts, developed two weeks after the adenoid removal. Henke's report of this case was very brief. In the discussion following the presentation of this case

Stenger<sup>25</sup> remarked, *er habe drei derartige in Anschluss an Adenotomie entstandene Fälle beobachtet* (he had observed three similar cases following adenotomy).

As far as I can make out these are the only references to sinus involvement after the operation. A description of my two cases follows:

CASE I.—October 4, 1910. L. H., 13 years old, referred to-day by her family physician for the removal of adenoids and tonsils. This was done on the same day. The following day the patient reported for observation and as everything looked clean the child was allowed to return home.

October 19. The patient is again brought in by her mother. Has fever and pain in the right ear. The mastoid is moderately sensitive. The lid of the left eye is swollen and there is some ptosis. Severe continuous, non-endurable frontal headache. Mother states that the child had fever as soon as it returned home.

There is pus in the left nose. X-ray examination shows a definite shadow over the left frontal sinus. Temperature, 38.8° C.

October 21. Operation.—Incision through the shaved eyebrow. Exposure of the periosteum. Formation of a periosteal bridge, according to Killian, 2 mm. wide. The bone appeared normal. On opening the frontal sinus over the inner end of the eyebrow thin yellow pus under high pressure escapes. Removal of the entire anterior bony wall. Laterally there is a deep recess which is cleaned out. The frontal sinus itself is partially filled with pus and polypoid granulations. Elevation of the periosteum of the orbital roof. Removal of the bony roof of the orbit. Curettage of the naso-frontal duct. The ethmoid cells, being healthy and normal, are left intact. Introduction of a fenestrated rubber drain from the nose. Primary suture of the skin incision. Bacteriological examination of the pus showed hemolytic streptococci.

October 25. The after treatment proceeded smoothly so that the drain was removed on November 17, and the patient discharged from the clinic. To-day the patient was obliged to return because of pain in the incision and rise of temperature. An incision was made into the scar and some pus was discharged.

December 12. Patient entirely healed and discharged.

CASE II.—H. S., 20 years old, complains of obstructed nasal breathing. Examination discloses a slight deviation of the septum, convexity toward the left side, hypertrophy of the right inferior turbinate, and an enlarged pharyngeal tonsil. Also enlarged faucial tonsils.

November 21, 1911. Under local anesthesia removal of the tonsils and adenoids. Not much bleeding.

November 24. The patient is free of pain. The wound surfaces appear to be in good condition but a very small remnant of adenoid tissue is seen to be hanging to the roof of the pharynx just behind the septum. This is not large enough to act as an obstruction to the breathing and for this reason is not removed.

December 7. The patient returns to-day and claims to have taken a cold a few days ago and that she has a discharge of pus from the left side of the nose. Rhinoscopy shows a fluid pus high up in the anterior portion of the middle meatus. The inferior turbinate and the anterior end of the middle turbinate are hyperemic and swollen. Temporary diagnosis, acute sinusitis of the anterior series of sinuses on the left side.

December 18. In the last ten days the patient has been treated in a conservative way with aspirin, menthol inhalations and cocainization of the anterior portion of the middle meatus. Fluid pus is always evident at the anterior end of the middle meatus. The floor of the frontal sinus is not especially sensitive to pressure. Irrigation of the left maxillary sinus is negative. X-ray examination shows a definite localized shadow in the left ethmoid region.

<sup>23</sup> Schönmann: Monatschr. f. Ohrenh., 1907.

<sup>24</sup> Putnam: Zentralbl. f. Laryngol., xxi, 207.

<sup>25</sup> Henke: Verhandl. des Vereins f. wissenschaftl. Heilkunde in Königsberg, 1910-1911.

<sup>26</sup> Stenger: *Ibid.*

Definite diagnosis: Suppuration of the left anterior ethmoid cells.

December 20. Pus is still present in the middle meatus. After cocainization the anterior end of the middle turbinate is removed.

December 29. Fluid pus is still present at the upper end of the middle meatus. Small polypi present in the middle meatus are removed. Examination with the fluorescent screen shows a healthy frontal sinus.

January 18, 1912. The nose is now free of pus. The lower turbinate on the left side is still swollen but as the patient has no further symptoms and breathes freely through her nose she is discharged.

### RÉSUMÉ.

How can we best interpret these histories? In the first place, both of these infections occurred in the second life decade; in patients 13 and 20 years old respectively, individuals in whom we know that the accessory sinuses have reached a full state of development. In the second place, both of these infections occurred in sinuses which drain into the middle meatus. In the third place, neither of these complications was observed until two or more weeks after operation. In the fourth place, the operation in the second case was inefficiently performed. All of these points, to my mind, are important.

First, as to the age of the patient. Although adenoids are not infrequently removed in adults the great majority of these operations are performed between the years of four and ten, in those years where the sinuses are still in an incomplete state of development. Meyer<sup>26</sup> says, *Die Empyeme der Nebenhöhle kommen fast nur bei Erwachsenen zur Beobachtung* (empyema of the sinuses is found almost exclusively in adults), and Wertheim,<sup>27</sup> who examined 360 cadavers for diseased sinuses, found the smallest percentage in the first decade and the largest percentage in the second decade of life. This explains, in part, why the sinus infections are among the rarer adenoid operation complications.

Second, both of these infections appeared in sinuses which drain into the middle meatus. How can we best explain this fact? The bacteriological examinations of the nose and the naso-pharynx have shown that these regions are not devoid of their bacterial flora. These microorganisms are usually non-pathogenic or if pathogenic they are of low virulence. The trauma of an operation can so increase the virulence of these organisms that we must count them as pathogenic. Brieger's work (*l. c.*) has shown that the bacteria from the wound surface of the naso-pharynx are driven through the nose by the acts of sneezing and blowing the nose. It is easily conceivable that some of this blood and infectious material can thus be driven into the ostia of the accessory sinuses.

Those sinuses which drain into the middle meatus of the nose are naturally more easily infected than those which drain into the *rima olfactoria*, inasmuch as we know that the current of expiratory air used in sneezing and in blowing the nose does

not usually rise above the free edge of the middle turbinate. For this reason the microorganisms of the infected blood and pus more easily reach and infect the frontal and maxillary sinuses and the anterior ethmoid cells than the sphenoidal sinus and the posterior ethmoid cells. Both of the cases cited in this paper have been infections of the anterior series of sinuses. We have, however, too few observations on this point to draw any definite or far-reaching conclusions.

Neither of these infections appeared immediately after operation, but after an interval of about two weeks. This has a very practical bearing for us. We must watch our patients longer after this operation than we have been in the habit of doing.

Finally, we must operate carefully and thoroughly in each case so that no shreds of adenoid tissue remain in the naso-pharynx after operation, for it is easily possible, although I cannot prove it objectively, that in my second case the incomplete operation was the cause of my post-operative infection. Certain it is that these remnants of adenoid tissue which are left in the naso-pharynx are very common causes of post-operative bleeding. Anyone who has closely observed the configuration of the naso-pharynx as shown by the X-ray plate, with a strongly flexed and a strongly extended head will have noted that the body of the atlas so projects into the cavity of the naso-pharynx, when the head is extended, as to form above it on the posterior wall of the naso-pharynx a distinct and deep pouch. It is practically impossible to totally remove the adenoid tissue in the depth of this pouch with the head in the extended position. However, with the head slightly flexed on the chest the posterior wall of the naso-pharynx becomes practically a plane from whose surface the adenoid tissue can be entirely removed. It is for this reason that I always advocate operating with the head of the patient slightly flexed.

In conclusion, how are we best to avoid, as far as possible, the complications of this so-called simple and very frequently performed operation. In the first place it would be well to operate when no local infectious processes were present in the nose, naso-pharynx or ear. We should do well, also, not to operate during local epidemics of the acute infectious diseases of childhood, especially if the patient had come into any sort of contact with children ill of these diseases.

Finally, we all realize that the ideal method of working is to make hospital cases of all these operations and to keep the patients under observation for a considerable period of time. This is practically impossible in all cases, but we can, nevertheless, keep our patients under observation for longer periods of time than is at present customary, especially if these patients are adults. If after two or three weeks no complications appear we can discharge the patients from our care.

In closing, I wish to say, in order not to be in any way misunderstood, that I advise the removal of an adenoid in any patient of any age where the diagnosis of one is made, but at the same time I wish to raise my voice in protest against the careless way in which this operation is so often performed and to call attention to the fact that serious and at times even life endangering complications of this operation are not infrequent.

<sup>26</sup> Schmidt-Meyer: *Die Krankheiten der oberen Luftwege*, Berlin, 1909.

<sup>27</sup> Wertheim: Cited by Zarniko, *Die Krankheiten der Nase und Nasenrachens*, Berlin, 1910.

# THE TRANSPLANTATION OF RIB CARTILAGE INTO PEDUNCULATED SKIN FLAPS. AN EXPERIMENTAL STUDY.<sup>1</sup>

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## INTRODUCTION.

The repair of mutilations or defects, such as those which involve the ears or nose, is attended with considerable difficulty.

In the treatment of such deformities it is often requisite to use flaps of tissue with skin on both sides. These flaps can be secured by one method or another, but it seems to me that the factor of chief importance is to provide a framework to support the flap which will secure the desired contour, and at the same time prevent shrinkage.

Many materials have been used for these supports, such as silver, gold, rubber, celluloid, etc., but all of them have the disadvantage of being foreign bodies.

A material is required which will not act as a foreign body; is easily obtainable; is rigid enough for the purpose, and at the same time can be shaped as desired.

In seeking for some suitable tissue in the body which would fulfil these conditions, I was led to undertake the experiments with costal cartilage which are outlined below.

Twenty-four experiments were carried out on 15 dogs. Animals between three months and two years old were used. Ether anesthesia was used in each experiment.

*Technic.*—The part was shaved, washed with green soap and water followed by alcohol, and then with ether. After the skin was thoroughly dry it was painted with tincture of iodine, 2.5 per cent. The iodine solution was also freely used in the open wounds and after suture of the skin. Fine black silk was the ligature and suture material used throughout.

In order to produce conditions of nutrition which would be similar to those in which the framework would be placed in actual clinical practice, I determined to transplant the cartilage into pedunculated skin flaps (Fig. 1).

A flap of the required size with either a broad or narrow base was outlined, and raised from its bed. It was then folded on itself, raw surface to raw surface, so that there was skin on both sides. The edges were held together with several sutures. In this way a sort of pouch was formed and into a selected portion of this pouch the cartilage was placed and secured.

The long flaps, with narrow bases, were dressed with gauze

moistened with normal salt solution, and each was protected from pressure by a moulded wire cage which was secured by a bandage. The short flaps, with broad bases, were in a number of instances exposed to the air without dressings.

## SOURCE OF CARTILAGE AND POSITION IN FLAP AFTER TRANSPLANTATION.

The cartilage was obtained from the cartilaginous ribs. The perichondrium was not disturbed except where shaping was done.

The cartilage was either imbedded in a thin layer of subcutaneous fat, or was placed in a pocket burrowed in the subcutaneous tissue itself, or was surrounded by the skin after the subcutaneous tissue had been removed.

The location of the cartilage varied in the different flaps. In some it was placed parallel to the base of the flap, either in the distal, intermediate, or proximal portions. In others, it was placed vertically to the base, and in different parts of the flap. In still others it was placed diagonally across the flap.

The shape of the cartilage varied. In some of the experiments it was inserted in its natural shape, and in others it was cut and moulded into the desired form.

## TYPES OF FLAPS.

The flaps when completed were either appendix-shaped, square, or rectangular, some of the latter having a broad and some a narrow base.

The completed appendix-shaped flaps were from 1 to 2 centimeters in diameter, and from 2.5 to 5 centimeters long. There was drying out of the skin, due to lack of blood supply, of from 1 to 1.5 centimeters of the tip of these flaps, when over 3.5 centimeters long. If the dried out skin was trimmed and the cartilage cut down slightly below it, the raw end would heal in a short time.

The bases of the finished square and rectangular flaps varied between 2 and 7 centimeters, and the length between 3 and 6 centimeters.

Some of the flaps were made with a curved border which was supported by a curved piece of cartilage.

The laxity of the skin made it possible to close immediately all of the defects left by raising the flaps.

## REMARKS.

Pieces of cartilage from 1.5 to 7 centimeters in length were used. The cartilage was allowed to remain in the flaps from 7 to 120 days.

In two instances where infection occurred the wounds were quickly brought into healthy condition, and the cartilage

<sup>1</sup> There are several reports on the clinical use of rib cartilage in the plastic repair of defects of the nose, and for the relief of laryngeal stenosis. In one instance rib cartilage was transplanted into an ankylosed elbow joint with some success. F. von Mangoldt: *Archiv f. klin. Chir.*, 1899, p. 926; *Verhandl. d. Deutsch. Gesellsch. f. Chir.*, 1900, p. 460. Nélaton and Ombredanne: *La Rhinoplastie*, 1904, S. 188, 284. A. Henle: *Zentralbl. f. Chir.*, 1904, p. 1233; *Mittel. a. d. Grenzgebiet d. Med. u. Chir.*, 1907, III, p. 161. Wegalowski: *Zentralbl. f. Chir.*, 1907, p. 449. J. F. Binnie: *Trans. Am. Surg. Assn.*, 1908, p. 379.





Fig. 1. Postoperative maps of different shapes of the transplanted cartilage. On removal of the cartilage the measurements were the same as at the time of transplantation, i.e. there was no sign of degeneration. No structural changes of the cartilage.

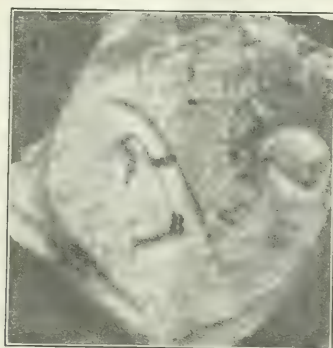


FIGURE 1.—Cartilage shape to form angle appeared in each type. (11-12, November 21, 1966). Specimen reported January 24, 1967. The cartilage is firmly healed in its new shape. Microscopic examination showed no signs of degeneration.



Figure 2 illustrates the morphology of the primary cultured cells. Cells, on a day 10, after the start of the subculturing stage, were found to be in the early transition stage. The morphology of the cells was not significantly different from that of the primary cells of the same species. No obvious change in the morphology of the cells was observed after the termination of the subculturing stage. The cells did not undergo the transition to a spindle-like morphology, proliferation, and formation of a cell mass, as observed in the primary cells. The cells did not undergo the transition to a spindle-like morphology, proliferation, and formation of a cell mass, as observed in the primary cells. The cells did not undergo the transition to a spindle-like morphology, proliferation, and formation of a cell mass, as observed in the primary cells.



saved, by the free use of tincture of iodine. In one experiment the cartilage was accidentally contaminated before transplantation, but after being dipped in the iodine solution it was placed in the flap, and per primam healing followed.

The appendix-shaped flaps containing cartilage, which were long and had comparatively narrow bases, were the least likely to be completely successful. The broad-based flaps, on the other hand, were nearly always successful throughout.

In several instances the cartilage transplanted in the flaps was obtained from other dogs, and these pieces were apparently as well nourished and gave as satisfactory results as those from the same animal.

The cartilage should be securely, but loosely, anchored in position. If there was pressure on any particular portion of the cartilage, as for instance by a tightly drawn suture, there was usually slight liquefaction and subsequent fracture of the cartilage at that point.

*Macroscopic examination* showed in every instance that the squarely cut ends of the transplanted cartilage had become slightly rounded. The healing was reactionless and the cartilage did not act as a foreign body.

The measurements of the cartilage when removed from the flap differed very little, if at all, from those taken at the time of transplantation.

On section the cartilage appeared normal and seemed well nourished (Fig. 2).

*Microscopic examination* showed the transplanted cartilage surrounded by a loose connective tissue zone containing blood vessels, which were more or less abundant, according to the length of time after transplantation. The cartilage cells appeared normal and there were no signs of degeneration or absorption.<sup>2</sup>

This series of experiments show that cartilage with its perichondrium may be successfully transplanted into flaps of the desired shape, with skin on both sides, so long as the pedicle supply is sufficient to nourish the flaps. The cartilage

<sup>2</sup> I take this opportunity of thanking Dr. C. D. Deming for assistance in the histological examinations.

may also be cut and moulded into any required form to support the flap (Fig. 3).

#### CONCLUSIONS.

From the results obtained in these experiments and from clinical experience, I feel sure that the transplantation of rib cartilage into skin flaps is a safe and promising procedure. Cartilage can be used with advantage in otoplasty, in the restorative operations made necessary by traumatism and disease. In microtia also much can be done, by the transference of a flap thus supported, in improving the condition due to arrested development. In rhinoplasty the cartilage support can be placed in a double-faced skin flap, from a distant part when it is formed, or can be inserted after the flap is in its new position. It is especially advantageous in the correction of saddle nose.<sup>3</sup>

As to the fate of the transplanted cartilage in these experiments, as far as can be seen the cartilage lives, is properly nourished and does not act as a foreign body. There has been no increase in length in any of the pieces transplanted.<sup>4</sup>

There is practically no absorption and there are no signs of degeneration, either macroscopically or microscopically. The cartilage shrinks very little, if any, up to four months, which is the longest period in the series, and it seems reasonable to believe that it will continue to be nourished and will live and act as a support as long as needed.

<sup>3</sup> In a case of my own, a strip of costal cartilage used for the correction of a saddle nose has remained intact for over two years. Bits of bone from the tibia, ribs and skull have been successfully used in the correction of saddle nose, and in rhinoplasty, but bone lacks plasticity, and on this account cannot always be used in reconstructive work.

<sup>4</sup> My results as to the fate of the transplanted cartilage do not coincide with those of Leopold (Arch. f. path. Anat. u. Physiologie, 1881, LXXXV, 310), and Zahn (cited by von Mangoldt, Verhandl. d. Deutsch. Gesellsch. f. Chir., 1899, p. 613). These authors transplanted experimentally very small slices of cartilage with its perichondrium, and found that adult cartilage degenerated and was absorbed. Von Mangoldt, on the other hand, found both clinically and experimentally that larger pieces of transplanted cartilage remained intact and were properly nourished.

## DENGUE, ITS HISTORY, SYMPTOMATOLOGY AND EPIDEMIOLOGY.\*

By DR. E. R. STITT.

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It is a remarkable fact that a disease so striking in its tendency to appear in wide-spread epidemics and with so characteristic a symptomatology should not have been reported until about 1780 and then almost simultaneously by Gaberti in Egypt, Bylon in Batavia, Rush in Philadelphia and a year of two later by Cubillas in Spain.

While Hirsch (Handbook of Geographical and Historical Pathology) gives the credit for the first mention of the disease

to the chronicler Gaberti, who describes a disease with certain resemblances to dengue as existing in Cairo in 1779, yet, for the reason that certain clinical features of this epidemic would hardly appear to belong to dengue, as we now know it, there would seem to be good ground upon which to give the credit of priority to our great American physician and statesman, Benjamin Rush, who, under the designation break-bone fever, gave us a true picture of dengue as it manifested itself in Philadelphia in 1780.

Gaberti was particularly impressed with the knee involve-

\* Paper read at a meeting of The Johns Hopkins Hospital Medical Society, February 3, 1913.



ment so that from his description the disease was known as the disease of the knees. He further noted swelling of the fingers and that the pains continued for more than a month. The sudden onset and the sweating would seem to belong to relapsing fever as well as to dengue and in support of the view that the disease described by Gaberti might have been relapsing fever we have the statement of Sandwith (Medical Diseases of Egypt) that bone pain, chiefly of the knee, is the symptom most complained of by the Egyptian native with relapsing fever.

Bylon, who reported an outbreak of an epidemic disease in Batavia in 1780, stated that everybody was attacked and that the symptoms were almost the same as those ushering in plague—headache, lassitude and pains in the joints. He noted, however, that this epidemic had no bad consequences, patients getting rid of it in three days under moderate diet and copious beverages.

Rush (Medical Inquiries and Observations, Philadelphia, 1789), in a chapter describing a bilious remitting fever, states that it first appeared in July and August, 1780.

Abstracting his description we note that hardly a family escaped and in many families scarcely a member. All ages were affected. The fever came on in different ways—in some a giddiness of the head marked the onset which attacked so suddenly as to produce even symptoms of apoplexy. It was a great surprise to Rush that persons so affected got well in two or three days. In some cases the onset came with delirium. The pain was exquisitely severe in the head, back and limbs. Pain in the forehead at times only occupied the eyeballs. In some cases the pains in the back and hips were so acute that the patient could not lie in bed. They all complained especially of soreness in the seats of their pains, particularly when in the eyeballs. The disease was thought by many to be a rheumatism, but its general name among all classes was break-bone fever. Nausea was common and in some instances vomiting occurred. There was a very disagreeable taste in the mouth. The exacerbations were more severe every other day. Relapses were frequent. A rash appeared on the third or fourth day which proved favorable. It was often accompanied by a burning of the palms of the hands and soles of the feet. Some who were not even confined to bed had these skin efflorescences. In some cases there were swellings under the jaw and about the ears. Discharges of blood from the nose frequently accompanied the fall of the fever on the third or fourth day while in others a profuse hæmorrhage from the nose or bowels about the eleventh day preceded a fatal issue. When the fever did not terminate on the third or fourth day it frequently ran on to the fourteenth or even the twentieth day with symptoms of typhus gravior. In some cases the fever was followed by jaundice. The fever declined in October when the weather became cool.

For treatment Rush recommended first a gentle vomit of tartar emetic which if given at the onset produced a crisis on the third or fourth day. If only nausea resulted he repeated the dose with the happiest effect. Salts and cream of tartar were given to open the bowels. After evacuating the stomach

and bowels he gave small doses of tartar emetic mixed with Glauber salts. Rest in bed was recommended as it favored the eruption of the rash. Persons who struggled against the fever, trying to shake it off by labor or exercise, had a slow recovery. He gave bark about the third or fourth day and if the fever continued beyond the fourth day he used blisters to the neck and behind the ears.

As the fever was sometimes accompanied by symptoms of dysentery opium was very beneficial after the necessary evacuations had been made. As the pulse was never hard, but only full, Rush never had recourse to bleeding. Many other physicians practised bleeding and he notes in this connection "I am bound to declare that I heard of several cases in which bleeding was followed by a fatal termination of the disease."

Most of those who recovered complained of nausea and loss of appetite with a bitter taste in the mouth. Faintness, especially upon sitting up in bed, was often noticed. The most remarkable symptom during convalescence was an uncommon dejection of spirits.

When we analyze this description by Rush it must be immediately apparent to every one that cases of typhoid fever (hæmorrhage from the bowels about the eleventh day), malarial fever (the exacerbations were more severe every other day), probably yellow fever (in several cases the fever was followed by a jaundice) and dysentery (the fever was sometimes accompanied by symptoms of dysentery) were confused with dengue, yet it is remarkable that notwithstanding this fact we should be given such a clear picture of the most striking features of the disease under consideration.

As I have seen the disease it would appear to me to be best outlined as follows:

I. A disease of strikingly sudden onset with rapidly rising temperature. Prodromata practically absent.

II. Very marked soreness deeply seated about the place of origin of the ocular muscles so that every movement of the eyeballs is at once complained of as giving pain.

III. General pains all over the body, more especially of the back and about tendinous insertions of the muscles which cause the pains to be referred to the joints. The rachialgia may be as great as that in variola or yellow fever.

IV. Fall of the fever about the third or fourth day which is often attended by a critical epistaxis, sweat or diarrhœa, to be succeeded by an intermission of from one to three days of a feeling of well being. About this time or with the secondary rise of fever the true dengue rash appears. This is at first noted about the bases of the thumbs and extending over the dorsal surfaces of the wrists. Almost simultaneously a measles-like rash appears over the dorsal and internal surfaces of the big toe extending to the ankle, especially over the internal malleolus. Later on the elbows and knees may be involved or the rash may cover thickly the entire body. A carmine flush of the palms of the hands and soles of the feet is not uncommon. The so-called primary eruption is nothing more than an initial flushing of the face.

V. About the third day a marked slowing of the pulse is

noted which may in the second accession of pyrexia be as low as forty-five beats per minute.

VI. There is a profound loss of appetite, interest and energy. These manifestations tend to extend well into convalescence. Insomnia or rather an inability to sleep for any extended period is often a marked feature of the disease. One dozes but does not sleep.

VII. There are no changes in the urinary findings which could be attributed to the disease.

VIII. Very characteristic is the blood picture, which may be well exhibited even by the second day. In one hundred cases in which I very carefully studied the blood the average leucocyte count was three thousand two hundred per cubic millimeter with a polymorphonuclear percentage of fifty-one. My lowest white count in this series was one thousand seven hundred and the lowest polymorphonuclear percentage twenty-nine. These results were obtained during a recent tour of duty in the Philippines. During a former tour I obtained lower results, but do not feel justified in attaching the same confidence to them as to those given above. These one hundred counts were made with a method in which the total count and the differential count were made in the same preparation. A one to twenty dilution of blood was made with  $\frac{1}{2}$  per cent of formalin in  $\frac{1}{2}$  per cent glycerin in distilled water to which diluent had been added one drop of Giemsa's stock solution for every cubic centimeter. The formalin (40 per cent formaldehyd) should have a reading of plus one to phenolphthalein.

It had been my opinion formerly that the differential count other than that of the polymorphonuclears was of diagnostic value. I am now convinced that the type of leucocyte making up the percentage not taken up by the polymorphonuclears is inconstant, there being at times an increase in lymphocytes while again the increase may be in the large mononuclears and transitionals.

A few months ago my attention was called to the rather marked leucopenia and low differential count of the polymorphonuclears in the blood examination of a case of undetermined fever in a lady living in Washington. I telephoned her attending physician asking him if the patient had been recently out of Washington. He gave the information that she had come up from Florida only a few days previously. I then asked whether she complained of an intense soreness at the back of the eyeballs, next as to the presence of an unusually slow pulse and then as to an eruption. The answers to the first two questions were in the affirmative, but to the last negative. I then requested him to look for an eruption commencing about the dorso-lateral surfaces of the thumbs and great toes. Two days later the eruption appeared confirming my suspicions.

This case was thought by her physician to be one of influenza and it is in the blood count and slow pulse that we have our best points of differential diagnosis. Sandwith notes the value of the slow pulse in differentiating the two diseases in Egypt.

At the present time with a railroad trip of only two days

separating us from Key West it will be appreciated how easy it would be for dengue cases to appear in the practice of the physicians of the North.

There have recently appeared many articles dealing with the question of the differentiation of dengue and various other dengue-like fevers such as phlebotomus fever, three-day fever, seven-day fever, sand-fly fever, etc., and, in many of these, great importance is attached to the characteristic of a slow pulse in them as compared with the more rapid pulse of dengue. This is an error, as I was more impressed by the constancy of the slow pulse in dengue than by any other symptom. In this connection it is remarkable that Rush makes no mention of a slow pulse in dengue because in his book on yellow fever (An Account of the Bilious Remitting Yellow Fever, 1794) the symptom which most attracted his attention was the slow pulse. In discussing at length the peculiarities of the pulse of yellow fever he states that he at first thought it due to some affection of the brain, but later ascribed it to a spasmodic affection accompanied with preternatural dilatation or contraction of the heart. Rush termed this pulse the indescribable or sulky pulse. He notes that it was present even in the very mild cases and he states that it was so familiar to him that he could have distinguished the disease without seeing the patient. It is remarkable that Touatre in his book on yellow fever should state that while physicians had observed the slowing of the pulse in yellow fever yet none understood its diagnostic value until Faget promulgated the law of the falling pulse.

Just here it may be noted that the most important consideration in connection with dengue is its differentiation from yellow fever. This differentiation rests best in:

(1) The normal urine of dengue and the albuminuria of yellow fever.

(2) The striking blood picture of leucopenia and marked diminution in polymorphonuclear percentage of dengue with normal findings in yellow fever.

(3) The jaundice appearing about the third day in yellow fever and the characteristic eruption in dengue showing itself from the third to the fifth day.

Many of the English authorities in India have drawn attention to the susceptibility of kala azar patients to intercurrent affections, and this they attribute to the marked leucopenia of kala azar. Of course with the much shorter duration of the period of leucopenia in dengue there would be less liability to bacterial infection, but in my opinion this possibility should not be lost sight of.

A vigorous man, a corporal in the U. S. Marine Corps, had an attack of dengue while suffering from an impetiginous staphylococcal infection. The fever continuing the man was sent to Canacao hospital, where he was found to have a positive blood culture for *Staphylococcus pyogenes aureus*. Fifteen days from the onset of the dengue the man died and at the autopsy numerous miliary abscesses were found in kidneys, spleen and liver. It would seem reasonable to consider that the lowering of the phagocytic forces enabled the local staphylococcal infection to become generalized.

It is possible that this susceptibility to infection may explain the occasional appearance of enlarged glands in dengue, infections from tonsils causing glandular enlargement. As a matter of personal observation I can state that I have very rarely noticed any glandular enlargements in dengue and this notwithstanding careful search in order to verify this finding, which is rather prominently brought out by some authorities.

Two of the most characteristic features of dengue were noted by Rush, viz.: the uncommon dejection of spirits and the slow recovery of those who struggled against the fever. It is a matter of common comment that the most frivolous person considers life a heavy burden during an attack of dengue—that the optimist becomes a rank pessimist. I can vouch for the statement that the only pleasure left to the dengue patient is the pleasure of solitude, there having been nothing I so desired while suffering from this disease as to be let alone. One of our naval officers suggested that an efficient method of ridding the service of practical jokers would be to furnish the dengue patients with large caliber revolvers and then persuade the jokers to have fun at the expense of the poor miserable dejected creatures.

The best proof of Rush's statement that struggling against the disease leads to a protracted convalescence is furnished by the experience of those on board the French ship *Cher* at the time of her being wrecked in New Caledonia, January 6, 1884. The accounts tell us that those who were in the first days of the disease did not want to be disturbed—they objected to being rescued. Others, however, who were recovering lent valuable assistance in the rescue work, but suffered, as a result, from a most protracted convalescence, some of them not having recovered their health two months later.

As regards the epidemiology of dengue there seems to be a general acceptance of the idea that dengue is transmitted by the common culicine mosquito of the tropics, *Culex fatigans*. There is not, however, that definiteness which attaches to the transmission of yellow fever by *Stegomyia calopus* or to pappataci fever by *Phlebotomus papatasi*, in both of which a certain period of development of the unknown filterable virus in the arthropod host is necessary before the insects become capable of transmitting the infections. It will be remembered that in the nine experiments as to dengue transmission, conducted by Ashburn and Craig, the authors threw out five of the cases for such reasons as previous immunity or refusal of the experimental mosquitoes to bite. Of the four remaining volunteers only one developed dengue. This man, however, had been on duty at the Division Hospital and the statement is made that he had not been exposed to the disease so far as could be determined. This of course rather militates against the value of this isolated experiment and furthermore the mosquitoes which bit him had fed on the blood of a dengue patient only two nights previously. If this is to be considered as a valid experiment, we must believe that only a short sojourn of the virus in the mosquito is requisite, which is rather at variance with the eleven days for the yellow fever virus and eight days for that of pappataci fever.

As regards the transmission of the disease by blood filtered through a diatomaceous filter it will be remembered that Ashburn and Craig, by proving this fact, placed the dengue virus in the same category with the filterable viruses of the two diseases just considered (Philippine Journal of Science, May, 1907). It should be stated that Doerr's report on pappataci fever was subsequent to that of Ashburn and Craig (Berlin Klin. Woch., 1908, No. 41).

Graham in Beirut carried out some experiments, one of which would seem to almost positively demonstrate mosquito transmission. He took mosquitoes which had fed on dengue patients, to a village in the mountains where no case of dengue existed. He caused these mosquitoes to feed on two natives of the village and both men became sick with dengue four and five days respectively after being bitten by the mosquitoes. Graham's claims to have noted piroplasma-like organisms in dengue blood have not been verified and do not receive credence (*J. Trop. Med.*, July 1, 1903).

The most convincing evidence as to mosquito transmission of dengue is that afforded by the absence of dengue in Port Said during the years 1906 and 1907 notwithstanding the prevalence of the disease in adjacent parts of Egypt. This was attributed to the absence of mosquitoes, these having been destroyed in the fight to make Port Said malaria free. This campaign was commenced in May, 1906 (Ross: *Ann. Trop. Med. and Parasitol.*, 1908, 11, 193).

While in the Philippines in 1905-1906 I was struck with the fact that when there were no mosquitoes about the hospital reservation there were no cross infections with dengue among the other and non-immune patients in the same ward. After the onset of the rainy season, however, mosquitoes became abundant and in all probability became infected and subsequently transferred the infection.

At this time I examined many hundreds of the mosquitoes present on our reservation and noted the presence of *Myzomyia ludlowi*, *Stegomyia scutellaris* and but one species of the genus *Culex*, *C. microannulatus*. The determination of the species was made by Prof. Banks, the entomologist of the Bureau of Science. I was not able at that time to find a single specimen of *Culex fatigans*.

In 1909 I returned to the Philippines and a few days after my arrival an officer who had been operated on for appendicitis suddenly developed a temperature. The blood findings reassured us from a surgical standpoint and by the third day of his fever the case was positively recognized as dengue. At the U. S. Naval Hospital, Canacao, P. I., there are two bungalow-type wards for sick officers. At the time I refer to one ward was perfectly screened, the second less satisfactorily. It was in this building that the case referred to above occurred. Three more similar cases occurring within a few weeks I had this building put out of commission and fumigated with sulphur. During the subsequent two years I remained at Canacao no further cases developed in this building, although dengue cases sent to the hospital from the station and ships were frequently under treatment in it.

In the hospital proper there are four large wards, each ward



thoroughly screened and in the two medical wards there are small wire-screened rooms or cages in which any case suspected of being malaria or dengue is immediately placed upon admission to the hospital. It is improbable that a mosquito can gain access to the main ward and almost an impossibility for such insects to effect an entrance into the wire screen cage.

Each of these compartments could accommodate nine beds. During the two years I followed this experiment, although more than 200 dengue patients were under treatment in these cages, there were no instances of infection of those lying in the open ward and only separated from the dengue patients by the wire screen.

## PROCEEDINGS OF SOCIETIES.

### THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

*December 2, 1912.*

#### Case of Friedreich's Ataxia. DR. H. M. THOMAS.

Dr. Thomas presented a case of Friedreich's ataxia from Dr. Barker's service. (Hospital No. 86096.) The history in short is as follows:

The patient is a young woman, 23 years old, who comes from a town in Maryland. No similar trouble has occurred in the family. Father is alive and well; mother died at 22 from dropsy. The parents were not related. There were no other children by that marriage. By the father's second marriage there are three half brothers and four half sisters. None of them have shown any sign of the trouble, and no such trouble is known in the patient's cousins or other relations. Tuberculosis has, however, occurred frequently in the mother's family.

The patient herself seems to have been a fairly healthy child; at least nothing was noticed until she was ten years old, when she had a low fever for a week or two. Directly after this her walk is said to have been extremely bad; in fact, it is stated that she had to learn to walk over again. After this her walk was never quite right, and for a number of years has gradually become worse. The patient herself, however, does not think there was very much wrong with it. She was able to walk to school. For the last three or four years it has been getting much worse, for the last year she has been unable to walk without some support, and for the last few months she has been confined to her bed. She has had no pain or other discomfort. She herself has noticed no particular change in her voice, and does not know when her feet began to become deformed.

In presenting the case, Dr. Thomas called attention to some of the salient points.

She is a small, rather poorly developed young woman. Her intelligence is practically normal. She is emotional, but is, as a rule, in a happy, contented frame of mind. Her voice is hesitating, somewhat indistinct and jerky.

The optic nerves are normal. The pupils react normally to light and contract during accommodation. In looking forward there is no nystagmus, but this occurs when the eyes are directed either to the right or the left. It is not of high grade. The other cranial nerves act normally.

When the patient sits with the back unsupported, one sees a constant, wobbling insecurity. This is perhaps most marked in the head.

The movements of the arms show the same static ataxia.

Muscular strength in arms is not materially affected. There is no local muscular atrophy. Sensation is normal. The triceps and biceps reflexes are not obtained.

The patient is entirely unable to stand alone, and when supported the irregular swaying of the body becomes pronounced.

The muscular strength of the legs is somewhat reduced, particularly the muscles moving the ankles. The legs are thin, and the feet are in a characteristic position. The arch of the foot is increased; the great toe is in constant dorsal flexion. Movements of the legs show ataxia. The knee jerks and ankle jerks are absent.

Sensation is, as a rule, not disturbed, although on the outer side of the right leg there is an area in which the responses are not as accurate as elsewhere. The sense of position of the joints is only slightly affected, and this in the small joints of the feet.

Plantar stimulation in both feet gives a definite increase in the already dorsally flexed great toes. This can also be brought about by descending tibial irritation.

The abdominal reflexes are active on both sides. There is a slight lateral curvature of the back.

The case presents a combination of symptoms that are considered characteristic of Friedreich's ataxia—the disturbed speech, nystagmus, static ataxia, great disturbance in walking, the characteristic deformity of the feet, slight lateral curvature, the absence of the deep reflexes with positive Babinski phenomena, slight sensory changes, and the retention of the abdominal reflexes.

The synonym, hereditary ataxia, is not applicable in this case, and, indeed, in Dr. Thomas' experience this has been true of most of the other cases seen in the Johns Hopkins Hospital. He knows of only one typical family in Maryland.

*December 2, 1912.*

#### Some Recent Work on Measles and Typhus Fever. DR. JOHN F. ANDERSON. (Washington, D. C.: U. S. Public Health Service.)

Our knowledge of the etiology of infectious diseases has advanced, not uniformly, but by leaps and bounds as new methods have been developed and new incentives have arisen.

With the evolution of a bacteriological technic, led by Pasteur and Koch, there was a rapid expansion in our knowledge of bacterial infections. The discovery that Texas fever of cattle was transmitted by the tick started extensive studies in the relation of insects to the transmission of disease. The demonstration that certain diseases are due to ultramicroscopic

organisms—so called “filterable viruses”—rapidly led to a study of many diseases of obscure etiology and cleared away much of the confusion regarding them.

Again, great epidemics have furnished the incentive for the most exhaustive study of some of our essentially epidemic diseases, as cholera, plague, influenza, meningitis, and poliomyelitis.

While very recent years have seen great advance in our knowledge of the phenomena of disease, and in our understanding of its physiology, there was a period not long since in which little was done to advance our knowledge of some important infectious diseases endemic almost throughout the civilized world, and research workers realize that new methods or agencies must be employed.

As a result of the use of certain methods or agencies of research, the value of which had not previously been generally recognized or employed, there has been in recent years a great increase in our knowledge of this class of diseases.

Along with these advances of our knowledge of those diseases considered for years as infectious has come the discovery that certain diseases formerly thought not to be communicable do, after all, belong to the infectious class. I refer especially to poliomyelitis, which for years was considered to be a degenerative disease of the nervous system and which recent researches have proved to belong among the infectious diseases.

The use of the monkey as an experimental animal, instead of the lower animals usually employed, has contributed more than any other factor to the important recent additions to our knowledge of the acute infections. Recent work has shown that the monkey is susceptible to a number of diseases that affect men and which are not readily transmissible or not at all to the small laboratory animals, such as rabbits, rats, and guinea pigs. We have thus been able to reproduce these diseases and to study them under laboratory conditions.

Another important advance was in the adoption of methods of experiment by which the infective material was introduced into the body so that it was brought into immediate contact with the organs or tissues primarily and most seriously affected in the natural disease, as in experimental meningitis and poliomyelitis, where the infective material is put directly into the cranial or spinal cavities.

Other factors of value have been the recognition of the fact that the same disease may present a very different clinical picture in one species as compared with another, even to a difference in post-mortem findings, and yet be due to the same etiological agent. Filtration through earthenware filters, by means of which contaminating organisms are removed; greater experience in interpreting results; the training and development of men for research; the foundation and endowment of institutions for research; all have contributed to what we know of the communicable diseases.

After this somewhat general discussion of the factors contributing to advances in our knowledge of the communicable diseases, I shall now discuss briefly some recent work on measles and typhus fever, especially that done by Dr. Joseph Goldberger and myself.

*Measles.*—Measles may be said to be practically a world-wide disease, one that is always endemic and often epidemic, especially in our larger cities. But in spite of the fearful toll in deaths that it yearly exacts, the large number of persons incapacitated for varying periods by illness, and the serious complications and sequelae, measles is too often regarded by physician and the laity as a necessary incident of childhood. The disease was the cause of 44,080 deaths in the registration area of the United States during the period 1900 to 1910. Its importance as compared with certain other diseases in the registration area during 1910 is shown in the following table:

DEATHS IN REGISTRATION AREA OF THE UNITED STATES IN 1910.

Disease	No. of Deaths	Deaths per 100,000
Diphtheria and croup.....	11,512	21.4
Measles .....	6,598	12.3
Scarlet fever.....	6,255	11.6
Whooping cough.....	6,146	11.4
Cerebrospinal meningitis.....	2,272	4.2
Infantile paralysis.....	1,459	2.7

While it has been quite the general belief among clinicians for years that the infective agent of measles is contained in the blood, in the nasal and buccal secretions, and perhaps in the “scabs,” the experimental data in support of this belief previous to 1911 were very incomplete.

Last year the work of Anderson and Goldberger on measles converted what had previously been opinions based on clinical observations into proven facts based on laboratory experiments. These authors showed that the monkey was susceptible to infection with measles by inoculation with blood from human cases of the disease. They showed that the apparent insusceptibility of the monkey to infection with measles was largely due to a limitation of the period of infectivity of the blood to the very early stage of the disease, before or shortly after the appearance of the eruption. Thirty-six hours after the first appearance of the eruption the infectivity of the blood for the monkey becomes greatly lessened and rapidly decreases. Studies on the nature of the virus as it exists in the circulating blood showed that the infective agent is capable in a certain proportion of cases of passing through a Berkefeld filter and therefore is included among the filterable viruses.

The virus resists drying for 24 hours, freezing for the same length of time, and is destroyed by heating at 55° C. for 15 minutes. Well monkeys, when placed in the cage with sick monkeys during the early stages of the disease, contracted measles after an incubation period of 5 to 11 days.

Experiments made to test the infectivity of the nasal and buccal secretions from human cases of measles showed that such secretions, collected within the first forty-eight hours after the appearance of the eruption, were infective for monkeys by subcutaneous inoculation; this would correspond to about the fourth and sixth days of the disease.

Experiments made to determine the duration of the infectivity of these secretions strongly suggested a reduction, if not a total loss of their infectivity with the approach of convalescence. Attempts were made without success to demonstrate

the presence of the infective agent of measles in the "scales" collected from human cases of the disease from 4 to 7 days after the appearance of the eruption.

Since the work of Anderson and Goldberger was reported, three papers by different workers have been published corroborating their results as to the presence of the virus in the blood of human cases and the susceptibility of the monkey to measles. Hektoen and Eggers, while chiefly concerned in their work on experimental measles in the monkey with a study of the leucocytes, state that the general results of their experiments agree very well with those reported by Anderson and Goldberger.

Nicolle and Conseil have reported the infection of the bonnet monkey with measles by the inoculation of blood drawn 24 hours before the appearance of the eruption. And more recently Lucas and Prizer have reported the observation of Koplik spots in monkeys experimentally infected with measles.

The results of these studies on measles give us our first definite information based on carefully controlled laboratory experiments as to the seat of the virus, its means of exit from the body and the probable avenue of infection. The experimental observations on the duration of infectivity of the secretions are in accord with previous clinical observations that cases of the disease are as a rule not infective after convalescence is well established. The great importance of this point and the further one as to the non-infectivity of the "scales" from a public health aspect can be readily appreciated.

*Typhus Fever.*—The last appearance of typhus fever in the United States in epidemic form was in New York in 1891-92. Since then, except for an occasional case at some of our large seaports, it was believed that the disease had been eradicated from this country.

It has been a subject of wonder to health authorities that, in spite of the occasional arrival in this country of immigrants sick with typhus and of many persons from endemic foci of the disease, typhus fever apparently did not gain a foothold in the United States. That this had already taken place has recently been shown through the demonstration by Goldberger and Anderson in the Hygienic Laboratory, U. S. Public Health Service, that a disease observed and studied in New York City by Dr. Nathan E. Brill is identical with typhus.

As far back as 1896 Brill began to notice from time to time among his typhoid cases types that were distinguishable from typhoid and paratyphoid fevers because of the short duration of the fever, the presence of a distinctive eruption and the absence of specific agglutination reactions. He continued his observations on this type of fever and published two papers based on the study of 255 cases observed up to December, 1910.

About the time that Dr. Brill's second paper appeared, Dr. Goldberger and I were engaged in the study of the typhus fever of Mexico and, having the picture of that disease clearly in mind, we were struck by the very marked clinical resemblance between it and the disease described by Brill. Influenced by this resemblance, we endeavored to determine,

if possible, the relationship between that infection and typhus fever.

Our efforts to do this were not successful until September, 1911, when we saw a well-marked case of Brill's disease in the wards of Mount Sinai Hospital, New York. Blood drawn from the arm vein of this patient was used for the inoculation of monkeys, one of which, 9 days after inoculation, developed a fever which reached its maximum 6 days later. The fever lasted 11 days, when it terminated by rapid lysis.

Blood was drawn from this animal at the height of its fever and successfully used for the inoculation of other monkeys.

Monkeys that have recovered from one attack are immune to subsequent infection. Since then the infection has been carried through 22 monkey generations by inoculation of blood, and is now being continued through guinea pigs.

Having established the susceptibility of the rhesus monkey to inoculation with defibrinated blood from cases of the disease described by Brill, it became important to determine the relationship of that disease to typhus fever; and for this purpose one of us proceeded to Mexico City, taking monkeys that had recovered from infection with the virus originally obtained from our Case No. 1 of Brill's disease, as well as fresh animals for controls.

Without going into details of our tests it is sufficient to state that 7 monkeys that had recovered from an infection with virus obtained from a case of Brill's disease were tested for their immunity to Mexican typhus, together with fresh animals. Of the 7 Brill-immune monkeys, not one showed any reaction as a result of inoculation with virulent typhus fever blood; while all 9 of the control animals developed the fever.

Ten monkeys that we had reason to believe to be resistant to Mexican typhus, and 8 fresh animals as controls, were tested for their susceptibility to Brill's disease. None of the Mexican typhus immune monkeys showed any indication of a reaction when inoculated with virulent blood, while 7 of the 8 control animals did react.

These results justified the conclusion that an attack of Brill's disease confers immunity to subsequent infection with Mexican typhus, and conversely, that an attack of typhus fever confers immunity to subsequent infection with Brill's disease. To put it in a simpler way, Brill's disease, so-called, and typhus fever are identical.

During the progress of the work necessary for the demonstration of the identity of the so-called Brill's disease and Mexican typhus we gave attention to various related problems. The particular one to which I refer is that of the mode of transmission. We found that the New York disease, as also the typhus of Mexico, may be transmitted from monkey to monkey by the bite of body lice that had been allowed to feed on monkeys sick with the disease; these results were in harmony with and confirm those previously reported by ourselves and others.

We were unable to transmit the disease by the bite of bed bugs, or by the inoculation of the buccal and pharyngeal secretions from a human case of typhus. I am convinced that



the only way by which typhus fever is transmitted is by the bite of the body louse, and possibly by that of the head louse.

Now that it is shown that typhus fever is identical with Brill's disease and that Brill's disease has been endemic in the city of New York for a great many years, there is a good reason to believe that what is true of New York is true also of other large American and Canadian cities. In fact, since our first work appeared, cases have been reported from several cities (Atlanta).

When one recalls how frequently the mild forms of even the familiar infectious diseases are overlooked it need occasion no surprise that the benign form of a disease, usually thought of in our country as an exotic plague or at least perhaps as a medical curiosity, should fail of recognition. That this is not applicable to typhus alone is strikingly shown by the history of pellagra and of hookworm disease in the United States.

I wish to point out that the recognition of these mild forms of typhus gives us a rational explanation of what Osler has well characterized as a "remarkable feature of typhus, namely, the occurrence of a few new cases at long intervals of time from any other outbreaks, and at great distance from any known foci of the disease. In other words, these mild forms constitute the missing epidemiological link between so-called sporadic cases or outbreaks. In the perpetuation of typhus this mild form plays somewhat the same rôle that the "missed" or the "carrier" cases do in such diseases as diphtheria and typhoid.

December 16, 1912.

Dr. H. M. Thomas exhibited three cases.

The first patient whom I shall show to you to-night presented himself to the Neurological Dispensary last July, complaining of a paralysis of one side of the body. He gave a history of having suffered from a paralytic stroke sometime back, but nothing else of importance; indeed, he considered himself well up to this incident.

Upon examination, a condition that interested us greatly was discovered. There was a loss of power on the left side of the usual hemiplegic type. The patient's walk, instead of being the usual spastic walk of the hemiplegic, has, as you see, on the left side the flaccid steppage gait characteristic of the paralysis in multiple sclerosis. The left arm, however, is somewhat spastic and held in a fairly characteristic manner. As I test the deep reflexes, you will see that those in the right arm are present, but that those in the left arm are quite markedly exaggerated. In the legs, however, neither the knee-jerk nor the ankle-jerk can be obtained on either side, and there is not the least sign of increased muscular tension in the left leg. The jaw-jerk is exaggerated.

Plantar stimulation gives on the left side a definite dorsal flexion of the great toe, while on the right side the stimulation is followed by a plantar flexion.

We have then a hemiplegic in whom the expected signs of spasticity are absent from the leg, even though the presence of a Babinski reflex indicates clearly that the pyramidal tract is affected.

The explanation of this was not clear until the routine examination revealed the fact that the patient was suffering from an unsuspected tabes. The lesion of this disease has implicated the posterior root fibres and destroyed the afferent part of the reflex arc of the legs. Sherrington has shown in his experiments on decerebrated and decapitated animals that the spasticity which develops under these circumstances depends upon the integrity of the segmental reflex mechanism, as do also the shortening and lengthening reflexes—those reflexes which give plasticity to the limbs. The spastic rigidity in hemiplegia is similarly conditioned, and could not occur in this case of tabes where the leg has, to use Sherrington's term, been de-afferented. In the arm the tabetic lesion has not destroyed the reflex arc, and we have here exaggerated reflexes and slight spasticity. The diagram on the board will indicate the condition of affairs.

The second patient Dr. Thomas showed was a young man 19 years old, who presented a very typical picture of progressive muscular dystrophy, associated with marked hypertrophy of certain of the muscle groups.

The third patient was a case of total left-sided facial paralysis, associated with complete deafness of the left ear, the condition following the administration of a dose of salvarsan for primary leuc infection.

Dr. Crowe demonstrated this case more in detail.

February 3, 1913.

Dr. E. R. Stitt read a paper on Dengue: see p. 117 of this issue.

#### DISCUSSION.

DR. GOLDBERGER: After Dr. Stitt's presentation I am in rather an embarrassing position. If I were permitted to discuss typhus or yellow fever, I might have something to say that he has not mentioned. The subject, however, has a great deal of practical interest to the American physician. Last summer there was a very extensive epidemic of dengue in Florida; in Tampa alone there were some 10,000 cases. Dengue, when mentioned, brings a smile to the listener, but I think Dr. Stitt's account is sufficiently convincing that the person suffering from an attack does not consider it a jest.

The mortality of the disease is almost nil. It does, however, produce a great reduction in vitality, and in places where an epidemic has occurred, the general death rate, subsequent thereto, is apt to rise. Aside from this, there is a great similarity between dengue and yellow fever. They are both mosquito-borne. The *Culex fatigans* is almost certainly the insect responsible for the dengue epidemics. Observations of epidemics and experiences such as Dr. Stitt reports permit of little doubt that the disease is transmitted by the mosquito. An epidemic of dengue is very much like an epidemic of yellow fever; but the epidemic of dengue spreads much more rapidly; in a given time the dengue epidemic reaches extensive proportions while that of yellow fever will still be relatively circumscribed. One explanation of this difference is that the "extrinsic" incubation in the mosquito *Culex fatigans* is not so long as that in the yellow fever mosquito.

Clinically there are other points, both of resemblance and difference. Dr. Stitt has brought these out very sharply. In field work, the question of differential diagnosis between yellow fever and dengue frequently comes up. The leucocyte count is very helpful, but for the field worker, not always available. He must only too frequently depend upon the clinical manifestations alone. In this connection there are one or two points I would like to emphasize. The slow pulse in dengue, that has been described by different observers. Personally, my own observation is not identical with that of Dr. Stitt. The pulse is not as slow in dengue as one would expect to find from the accounts of this disease. But such things are relative. It is not as slow as in yellow fever, though no doubt slower than in many of the common febrile states; such as influenza, for example, with which, by the way, it is not uncommonly confused.

There is one other point, and that is the short intermission that occurs in dengue and also in yellow fever, not very definitely emphasized in the literature so far as yellow fever is concerned. There may be a rapid rise in the temperature for the first twenty-four hours succeeded by a fall to normal, then a second rise. I have seen cases of this kind with an intermission of from four to twelve hours; it is very confusing, especially in the South. It suggests malaria.

Now for the differential points in the two fevers! There is no difficulty in recognizing a fully marked case of dengue—the picture is complete. The same in yellow fever. They are just as easy to recognize as is a case of pneumonia.

The difficulty arises when you come to deal with a case not well defined, and we meet with such cases more often than might be supposed. If we had a case without decided leukopenia, no eruption, and a slight albuminuria, the latter would suggest yellow fever. The practitioner of the South would hesitate to call such a case yellow fever; he would rather call it dengue. How should he avoid making that mistake, consciously or unconsciously? If he compares the two diseases, type for type, he will find it much easier to arrive at a differentiation. If he takes a case of dengue with a sharp rise and run of fever, say 103 or 104, and compares it with one of yellow fever of the same degree, the latter would show other characteristics, notably jaundice and a pulse rate down to 50 or 60. With a picture of that sort you ought to have no difficulty in telling dengue from yellow fever. In the absence of jaundice and hemorrhagic symptoms, except for the not invariable leukopenia, there is no real way of deciding. If the eruption is present, you would say it is dengue, but often the eruption is absent. In about 50 per

cent of the cases no eruption appears. The only thing to do as a safeguard is to put all cases of fever under a mosquito bar and wait for developments. Even then the diagnosis may have to be deferred. In southern countries, if one runs across a case of fever, the safe and rational thing to do always is to put it under a mosquito bar. Mild, imperfectly defined cases are undiagnosable except by waiting for graver cases to occur.

DR. STITT: I must say that I possibly brought out the occurrence of the slow pulse in dengue somewhat stronger than I should have for the reason that I wanted to work in Rush's observation of the slow pulse of yellow fever. Dr. Carter represents the pulse relationship between dengue and yellow fever as it exists in the United States. In the Philippines, in the matter of differentiation between influenza and dengue, the slow pulse is of importance. In the first day of the attack of dengue the pulse will be about 100. For the first two or three days it will stay between 90 and 100—then, with the first drop and going on into the second febrile paroxysm, it will be down to 60 or 65.

DR. H. R. CARTER: I have seen no dengue since 1904. At that time I think none of us knew of the particular help of the blood picture in diagnosis. I did not, at any rate. As regards the pulse rate, I agree with Dr. Goldberger; I think it differs considerably in different parts of the country. In the great epidemic of '97-'98 in Texas and Louisiana, there was no slowness of the pulse with the first fever; it always fell in the intermission and in the second rise of fever the pulse continued slow. The same in the Key West epidemic of '95. I would quote: during the first fever the pulse falls markedly when the fever goes down, and does not rise with the second fever. In the clinical differential diagnosis with yellow fever and dengue, I think (I am not speaking of the blood picture), I think no one can see any difference between them in the beginning, because there is no difference between them in the beginning. Dr. — who has had a large experience in yellow fever, I saw make mistake after mistake, because he did not wait. Both begin with red face, with red gums, and conjunctivæ; with a ridged tongue; both of them begin with active congestion of the mucous membranes and skin. For 24, 36, or even 48 hours there is no difference between the faces of dengue and yellow fever.

Dr. Goldberger is perfectly right as to the difficulty of diagnosis from appearances the first day, for you don't know whether it is yellow fever or whether it is dengue. You cannot tell until the next day.

## JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice: abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXIV is now in progress. The subscription price is \$2.00 per year.

(Foreign postage, 50 cents.) Price of cloth-bound volumes, \$2.50 each.

A complete index to Vol. I-XVI of the Bulletin has been issued. Price 50 cents, bound in cloth.

## NOTES ON NEW BOOKS.

*The Prospective Mother. A Handbook for Women during Pregnancy.* By J. MORRIS SLEMONS, Associate Professor of Obstetrics, Johns Hopkins University. (New York and London: D. Appleton & Co., 1912.)

In his preface the author of this excellent little volume tells us that it is written for the use of women with no special knowledge of medicine to answer questions which may occur to them concerning the general hygienic measures for safe-guarding their health during pregnancy. When one considers the vast number of books now published on questions relating to sex, reproduction, etc., and advertised in a lurid style (to which they owe their sale) in journals read by women, this work will fill a long felt want, for it is written in a manner that one most ignorant on technical subjects cannot fail to understand it.

The subject is treated under twelve chapters, with the following headings: I. The signs of pregnancy and date of confinement. II. Development of the ovum. III. The embryo. IV. The food requirements during pregnancy. V. The care of the body. VI. General hygienic measures. VII. Ailments in pregnancy. VIII. Miscarriage. IX. Preparation for confinement. X. The birth of the child. XI. The lying-in period. XII. The nursing mother.

The only chapters to which the reviewer can offer anything in the light of adverse criticism are those upon the development of the ovum and the embryo. The author admits that these subjects do not readily lend themselves to a popular description, and although he has handled them with remarkable skill it is doubtful that the average woman will be able to obtain much of an idea of some of the extremely complicated problems of embryology, after reading this portion of the work. It would probably be impossible to write such a book without some reference to these subjects and unquestionably if some of the main principles of embryology and development are understood the prospective mother will be able more rationally to care for herself and her unborn child. For these reasons the chapters mentioned are in no way out of place.

The rest of the work deserves the highest praise. Too much cannot be said of the excellent points brought out in the chapters referring to the food requirements, care of the body and general hygienic measures; as the writer here clearly demonstrates his familiarity with the chemistry of physiologic metabolism. He is positive in his advice that every prospective mother should be under competent medical supervision from the outset.

In the chapter on miscarriage, there is much of material value upon the medico-legal and moral aspects of abortion. It is sometimes surprising to the practising obstetrician to find that a woman of high moral education and training is entirely ignorant upon this important question. That this ignorance is feigned in many instances for personal convenience must be admitted, yet, even among the better educated such is frequently the case. To those who need instruction upon this point no better reading can be offered than that contained in the volume under consideration.

The chapters dealing with labor are extremely carefully written and contain much of great practical value to the prospective patient. The importance and reasons for sterilization are thoroughly gone into and not a little space is allotted to a brief résumé of the history of antiseptics in obstetrics, so that the reader may thoroughly appreciate its true significance. The advice that cases in which trouble may be expected can be best treated in a well-regulated hospital will markedly appeal to the practising physician, who has been handicapped by the inconvenience of the home in such instances. The same may be said of the author's advice against the employment of untrained or partially trained nurses.

Much more might be said of many of the excellent features of the work. There is nothing whatsoever in the text that is calculated to arouse the fears of the nervous individual and where it is necessary to refer to some of the more disagreeable features of

the condition the author has been extremely careful in his choice of language, and there is nothing that might offend or cause apprehension to the most sensitive.

Obstetricians will find it a most valuable book to place in the hands of their patients.

*Pharmacology and Therapeutics for Students and Practitioners of Medicine.* By H. C. WOONS, JR., M.D. \$4. (Philadelphia and London: J. B. Lippincott Company, 1912.)

The subject matter of this 413-page volume is arranged in chapters as follows: Chapter I. General pharmacological and therapeutic considerations. II. Drugs used to affect secretions. III. Drugs used to affect nervous system. IV. Drugs used to affect circulation. V. Drugs used to affect alimentary tract. VI. Drugs affecting metabolic processes. VII. Drugs acting on causes of disease. VIII. Extravenous remedies. IX. Drugs of minor importance.

Although the drugs are dealt with in a systematized way pharmacologically, no systematic consideration of the treatment of disease is given. The usual therapeutic procedures, such as paracentesis (abdominal or thoracic), introduction of nitrogen into the pleural cavity, intraspinal injection of serum, strapping the chest wall, etc., etc., are not described; nor does the work deal with vaccine serum, hydro, mechano, or psychotherapy. No therapeutic index is appended, therefore the information wanted by the therapist is not always readily found. The subject matter relating to therapeutics is not always sufficiently detailed, as for instance in the section dealing with the administration of salvarsan. In this latter connection it was noted that the dose recommended is only one-tenth of that usually employed for adult males. The book therefore is one of pharmacology and does not justify the "Therapeutics" which is included in the title.

As a work on pharmacology, though perhaps somewhat elementary, it will be found of considerable value to students and to the practicing physician.

L. G. R.

*Skin Grafting for Surgeons and General Practitioners.* By LEONARD FREEMAN, M.D. Illustrated. \$1.50. (St. Louis: C. V. Mosby Company, 1912.)

This monograph considers in a brief way the general subject of skin grafting. It is divided into 12 chapters, as follows: I. Terminology. II. Comparative Vitality of Grafts from the Old and from the Young. Heterogeneous Grafting. Dangers of Transferring Disease. Influence of the Patient's General Condition upon Skin Grafting. Surgical Cleanliness. III. The Method of Reverdin. IV. The Method of Thiersch. Its use in Special Cases. V. The Wolfe-Krause Method. VI. The Method of Hirschberg. Skin-Periosteum-Bone Grafts. VII. The Transplantation of Mucous Membrane. Anomalies in Skin Grafting. Sponge Grafting. VIII. Grafting from Animals. IX. Grafting in Lupus, in X-ray Burns, on the Cranium, and in Connection with the Eye and Ear. X. Local Anesthesia in Skin Grafting. XI. Histology and Pathology. XII. Brief Comparison of Different Methods of Skin Grafting.

There is little in the text which is not familiar to those who are conversant with the subject, and there are few, if any, original ideas advanced by the author.

The references are well chosen and full credit is given to those whose papers have been consulted in the preparation of the work. The book is well written and nicely gotten up.

It is a timely contribution, as there is no other book written in English which deals entirely with skin grafting. It will be of particular value to those who do grafting only occasionally, as it contains in a short space the best ideas on the subject.

J. S. D.



*Tuberculin in Diagnosis and Treatment.* By LOUIS HAMMAN, M. D., and SAMUEL WOLMAN, M. D. (New York: D. Appleton & Co., 1912.)

American students of tuberculosis and sanatorium physicians should greet this book gladly. It is the third work on tuberculin in English that has appeared in 1912, but far more valuable and complete than either the translation of Sahli's *Tuberculin Treatment* or the small book by Rivière and Morland, which have only a provincial character.

The authors disclaim the intent to produce a book for specialists or to present a complete review of the literature. Nevertheless they have fairly accomplished these purposes, for they have fully discussed what is known of the principles of tuberculin action and in the last two chapters covered all of importance in its use for diagnosis and treatment. It is therefore a very useful book to the specialist to whom the foreign literature is not accessible.

The liberal quotation from Koch's first paper on tuberculin is well chosen, but in the translation the word "vaccinate" would be better rendered "inoculate." In the first chapter the reader is clearly shown the evidence, so long unappreciated, that tuberculin reaction does not necessarily mean disease in the clinical sense. The literature on the nature of the tuberculin reaction and its explanation as related to anaphylaxis is well covered. In this chapter the words proteid and protein are used interchangeably, though the latter is preferable. A few errors in interpretation of the literature are of minor import. On page 56 it is stated that tuberculin never sensitizes normal animals. While this is true of the skin, they may suffer anaphylactic shock. The summary of the relation of hypersensitiveness to immunity in tuberculosis is very timely. The reproduction of Roemer's temperature charts aids in fixing the principles, and what will impress a reader familiar with the subject from the experimental side is the clearness with which the authors have grasped the meaning of these and set forth their clinical application. The majority of medical readers who will peruse this book because of their interest in tuberculin should not neglect this important chapter.

Under the "Use of Tuberculin in Diagnosis" all forms of the test are well explained. From the ample clinical experience of the authors they argue for the retention of the conjunctival test as an aid to separating clinical tuberculosis from old healed infections. Doubtless they realize its general abandonment since they freely discuss its disadvantages. Its usefulness is debatable. The subcutaneous test is advised only for focal reactions and not to exceed 5 mg. (a most desirable rule in the opinion of the reviewer, though he would use it for a final exclusion test in the absence of cutaneous reactions). The selection of a maximal dose is wisely judged to be dependent on the desire to exclude active tuberculosis.

Excellent rules are given for making the tests, but more retention of the wide variation in strength of tuberculins due to imperfect standardization—especially in America—would be desirable. The intracutaneous test is regarded as too delicate for diagnosis but more valuable than the cutaneous as a measure of hypersensitiveness. Tables of statistics of the various tests in relation to age, etc., add to a very complete review of the subject. Too much space relatively is devoted to the discussion of Detre's alleged differential human-bovine test which *a priori* never deserved serious attention. The estimate of the uncertain value of quantitative tests is commendable, the repetition of the limitations of tuberculin in diagnosis is most admirable, and its dangers fairly argued out of court by wise cautions.

The chapter on the use of tuberculin in treatment takes up the methods of preparation, details the various kinds, their chemistry, results of experiments and clinical results. Under "Methods of Administration" the authors give their own methods and experi-

ences, introducing typical charts and illustrative cases of great practical value to physicians who would embark on this therapy. They are exponents of the gradual or "timid" method of Trudeau and Sahli and give cogent reasons for it, sometimes in colloquial, picturesque phrases. They believe in mild focal reactions and that the best rationale is found in a stimulation of the foci by increasing doses and are convinced that their results are good. They do not publish their own statistics thus far but give full references to others and discuss the proper basis for judging results.

Taken as a whole, the literature has been thoroughly culled and full references are given on each page. A few errors are noted in the description of tuberculins. Under Von Ruck's "Watery Extract" is given the method of making the so-called "antiphthisin" on page 217. For "Endotin or Moeller's Tuberculin" is evidently meant Gabrilowitsch's, page 221. On page 70, "glow-worm" should be "slowworm." A few other words stare at a proof reader, yet it is needless to specify. Incidentally the reviewer must not omit to congratulate the authors upon their good style and command of vocabulary which rank the book in a literary class above the average.

*Surgical Operations with Local Anesthesia.* By ARTHUR E. HERTZLER, M. D. Kansas City, Mo. Price \$2.00. (New York: 91 William Street. Surgery Publishing Company, 1912.)

The author says in the preface that his object in writing the book is to furnish in a convenient form the technic of some of the commoner operations that can be done in a satisfactory manner under local anesthesia. For the most part he presents his own methods. He considers the general principles of local anesthesia and the technic of administration; the drugs employed and their use in the various regions of the body.

The book is well printed and nicely gotten up. The marginal notes are convenient. This monograph will be of interest to surgeons as it contains many valuable suggestions, and should be especially useful to the general practitioner, who is occasionally called upon to perform minor operations under local anesthesia. J. S. D.

*Minor Surgery.* By LEONARD A. BIDWELL, F. R. C. S., etc. Second Edition. Revised and enlarged. Illustrated. Price \$3.75. (London: University of London Press; New York: Oxford University Press, 1912.)

The first edition of this book was reviewed last year in the May number of the Bulletin. There is little to add to what was said at that time, except that the second edition is larger and is much improved in appearance.

There has been considerable advantageous revision of the text, and a chapter on Bandaging, Strapping and Minor Injuries has been added. J. S. D.

*A History of Nursing from the Earliest Times to the Present Day with Special Reference to the Work of the Past Thirty Years.* Edited and in part written by LAVINIA L. DOCK, R. N. In four volumes. Vols. iii-iv. (New York and London: G. P. Putnam's Sons, Publishers, 1913.)

The first and second volumes of this most comprehensive work were prepared by Miss Nutting and Miss Dock. The present volumes it will be seen are issued under the editorial supervision of Miss Dock, assisted by many willing workers, in every country. The completed work furnishes a full and detailed account of the present state of nursing throughout the world and is worthy of all praise.

The volumes before us contain voluminous chapters on the "Nurses of Great Britain and Ireland," on the "Growth of Nursing in the United States," on "Nursing in the Countries of Europe,"

on the "Revolution in French Hospitals," on the "Rise of the German Free Sisters," on "Pioneer Work in Switzerland, Holland and Belgium," on "Modern Nursing in an Ancient Setting" (Nursing in Italy and Spain), on "Nursing in New Continents" (Canada, Newfoundland, Australia, New Zealand and Africa," on "Nursing Sisters of the Orient" (India, China, Corea, Japan), and finally on "Some Island Hospitals and Nurses" (Cuba, Porto Rico and the Philippines).

The record is marvelously interesting and the tale of the labors of heroic and self-sacrificing women is inspiring. The only omissions worthy of note are similar accounts of nursing in the Canal zone and in Mexico. The chapter on the growth of nursing in the United States traces in great detail the steps which have been taken by the wise promoters of the movement in this country to produce the practical and educational conditions which in the past twenty years have transformed our training schools and unified the profession of nursing. Adequate tributes are paid to the women who furnished the brains to direct and the ideas through which others have wrought out great improvements. The volumes are finely illustrated and attractively presented. Miss Dock is to be congratulated upon the success of her laborious undertaking.

Every person interested in the development of nursing should possess a copy of this monumental work.

*Surgery and Diseases of the Mouth and Jaws.* By VILRAY PAPIN BLAIR, M. D. Professor of Oral Surgery in the Washington Dental School. Illustrated. (St. Louis: C. V. Mosby Company, 1912.)

The author says that in spite of all the special work that has been done in the study of the mouth and allied structures, the ordinary standard of surgical treatment given to diseases and deformities of the mouth does not equal that attained in other regions of the body. His idea in undertaking the work is to present the more pertinent observations of the constructive workers in the medical and dental profession. He has succeeded admirably in his object.

The book contains 44 chapters and is well planned and nicely printed. The numerous illustrations are excellent. It is an interesting practical study of the subject, and will be of special value to the operating surgeon.

J. S. D.

*The Development of the Human Body. A Manual of Human Embryology.* By J. PLAYFAIR McMURRICH, M. D., etc. Fourth Edition, Revised and Enlarged. (Philadelphia: P. Blakiston's Son & Co., 1913.)

All who know this excellent embryology will welcome the new edition, which has been brought up to date. It is the best English manual on this subject, and for the average student is sufficient, without being superficial or incomplete; it furnishes him a thorough grounding in a difficult science, and is so written as to be attractive—a difficult task in a branch of medicine which seems unusually dull and hard to the beginner.

*Napoleon's Campaign in Russia, Anno 1812. Medico-Historical.* By DR. A. ROSE. (New York: Published by the Author, 1913.)

Medical students unfamiliar with the history of this campaign will find a vivid account of it in this small volume of Dr. Rose, who has gathered together various reports by doctors and others who accompanied the army. The sufferings of the soldiers were horrible; they lacked food and clothing; had to endure frightful cold, and were in want of all proper medical care. Probably no army of the size of Napoleon's ever went through such a hideous campaign, and it is to be hoped that no army will ever again have to endure what it did. Such a picture of needless suffering and waste of life should make all readers strong peace advocates. It is to be regretted that Dr. Rose did not draw more fully on such

published medical accounts as exist of this campaign, for from a medical point of view it is one of exceptional interest. Napoleon always tried to take the best care possible of his soldiers and it would be most interesting, if such documents exist, to know the exact medical arrangements made beforehand for this campaign. Larrey, the great surgeon, whom Napoleon admired above almost all his associates, accompanied him on the journey to Moscow and one longs to know more about what Larrey, the most humane of men, did for the soldiers.

*Golden Rules of Surgery.* By AUGUSTUS CHARLES BERNAYS, M. D., etc. Second Edition. Revised and Rewritten by WILLIAM THOMAS COUGHLIN, M. D. \$2.50. (St. Louis: C. V. Mosby Company, 1913.)

This is one of the volumes of the Golden Rule Series. Dr. Bernays was a brilliant surgeon in St. Louis, and his book of rules has its value. He copied many of them from a selection made by Fenwick, an English surgeon, and now the volume undergoes a third revamping. Students who try to learn surgery or any other branch of medicine by "golden rules" will not advance far, and these volumes should be used only in conjunction with the larger treatises on surgery, medicine, etc.

*Vaccine Therapy and Opsonic Treatment.* By R. W. ALLEN, M. D., B. S. (Lond.). \$3. Fourth Edition. (Philadelphia: P. Blakiston's Son & Co., 1913.)

The merits of this work were noted, on the appearance of its second edition, in the Bulletin of March, 1909. A third edition was published in 1910, and the author now deems it necessary to rewrite the work in great measure and enlarge it, for the same reason that the third edition was called out, namely "the great developments and extensions which have been made in vaccine therapy" since the last issue. For laboratory workers this is a most useful book, for the author has collected much information on the use of vaccines in a large number of diseases, and describes clearly the proper administration of these bodies. The general practitioner, on the other hand, will possibly get a somewhat false idea of the value of vaccines from reading Dr. Allen's book, and should be cautious in recommending their administration, except by some physician who has made himself expert in this line of work. Whatever the further results of study may prove as to the real value of vaccines in a variety of diseases, this book, at the present time, is both serviceable and important.

*Diet and Hygiene in Diseases of the Skin.* By L. DUNCAN BULKLEY, M. D. (New York: Paul B. Hoeber, 1913.)

There is no question that in diseases of the skin diet plays a most important rôle and Dr. Bulkley, from his very large experience, treats this subject in a simple, clear and authoritative manner. He first lays down certain general principles underlying the treatment of skin affections in general, and then takes up more particularly some of the commoner diseases. The book is composed in large part of lectures delivered to post-graduate students. The author has not attempted to write a large comprehensive treatise but rather to summarize the results of his own practice, and for the general practitioner the book is a good one.

*Internal Medicine.* By DAVID BOVAIRD, JR., M. D., etc. Illustrated. \$5. (Philadelphia and London: J. B. Lippincott Company, 1912.)

This work is a good abridged summary of most of the latest work on internal medicine. It is well proportioned but all much too brief to warrant its title.

The book would be of value to the junior student or busy practitioner and could well be termed "a student's manual of internal medicine."

*Health Through Rational Diet.* By ARNOLD LORAND, M. D. (Carlsbad). \$2.50. (Philadelphia: F. A. Davis Company, 1912.)

Many a book has won a success by being introduced to the public by a man of established reputation for great ability. We fear, however, that Dr. Victor C. Vaughan's introductory words will not suffice to persuade the profession at large to buy Dr. Lorand's work. The author is known to many travelers as one of the leading practitioners at Carlsbad. Were it not for this sort of international reputation it is questionable whether his book would have been translated. Boiled down to one-third its present size, it would serve a sufficiently good purpose of telling the uninitiated something about foods, diet, and health. In its present form it may help and amuse, for it is written in a pleasant light style, those who have time to read it, but it cannot be considered as a text-book for students. It is a popular work, in the sense above indicated, that it is written for a leisure class, such as those who have to go to Carlsbad to restore their over-worked digestive tracts.

*Medical Men and the Law.* By HUGH EMMETT CULBERTSON. (Philadelphia and New York: Lea & Febiger, 1912.)

Many physicians will welcome this book, and we also are glad to welcome it. The author is a member of the Ohio and New York bars, and he has compiled an excellent work on the "legal rights, duties, and liabilities of physicians and surgeons." While the statutes of many of the states vary on these very points yet there is often need for a physician or surgeon to be able to refer to a legal book which makes these plain to him, and here we have it. This book will not relieve a doctor of the necessity of seeking a lawyer's advice, in case of a medico-legal suit or trial, but it will aid him by showing him how similar cases have been decided in various states. The author has divided his work into the following chapters: Definitions, Who May Practise Medicine and Surgery, Relation of Physician to Patient, Compensation, Malpractice or Negligence, Criminal Liability of Physicians and Surgeons, Exemptions of Physicians and Surgeons, Physicians and Surgeons as Witnesses, Right to Protect Professional Reputation, Validity of Contract Restricting Exercise of Profession, and Wills. Any large practitioner is likely to have to meet one or more of these problems not infrequently, and unless he has had exceptional advantages, he will be at a loss to know what is the correct attitude for him to assume in some trying positions. He will be much aided by a careful perusal of this well written treatise, one not marred by legal technicalities of phrase, which so often make a legal judgment difficult of comprehension to the average reader.

*Oxford Medical Publications: The Surgery of the Rectum for Practitioners.* By SIR FREDERICK WALLIS, M.B., etc. (London: Henry Frowde and Hodder & Stoughton, 1912.)

This book is so similar in general to the numerous other text-books on the same subject in English, that one wonders a bit at the need for such reduplication of effort. Like the rest it begins with a chapter on regional anatomy, which is the weakest part of this particular volume, and might well be left out of all such books. The usual rectal diseases are taken up in successive chapters and are satisfactorily discussed. The book is well written and the author shows a commendable tendency to delete from his text many of the traditional classifications and procedures that are becoming obsolete. The important facts are presented clearly and with discrimination.

Certain features are noteworthy as distinguished from the ordinary content of works on rectal surgery. Wallis attaches great importance to the value of zinc cataphoresis produced by a rectal electrode in extensive and obstinate ulcerative colitis, and in the palliative treatment of carcinoma. Emphasis is laid

on the relation of certain cases of colitis and proctitis to arthritis, and illustrative cases are cited in which the joint trouble has disappeared with the cure of the rectal condition. It is of interest that this author regards syphilitic stricture of the rectum as much rarer than is usually thought to be the case.

Great importance is attached to lesions of the delicate membrane at the ano-rectal margin, most of the inflammatory diseases as peri-rectal abscess, fistula, etc., being attributed to such portals of entry. The chapter on abscesses is particularly good, but one notes that this surgeon does not disturb the sphincter in acute abscesses in any case, and admits tacitly a high proportion of secondary fistulae.

Unlike many proctologists, Wallis is a believer in the radical excision of hemorrhoids, the Whitehead operation and its modifications—with the proper qualification that it be employed where the indications justify it and not as an invariable routine. On one point in the discussion of this method issue may be taken with the writer. In disposing of the objections to the Whitehead operation, the contention that the removal of the mucosa renders the sense of warning less acute and hence entails a certain amount of rectal insecurity, is declared to be an "absolute fiction." An investigation of the late results of Whitehead's performed in this hospital, especially in the case of one or two unusually intelligent patients, convinces the reviewer that in rare instances this "fiction" is unfortunately true.

On the whole the book is clear and well balanced, being free from the padding with voluminous and unnecessary detail so common to this type of work. It meets the purpose for which it is expressly designed better than is usual. H. B. S.

*Safeguarding the Special Senses.* By HENRY O. REIK, M.D., etc. Illustrated. 75 cents. (Philadelphia: F. A. Davis Company, 1912.)

The sub-title of this small, neatly printed volume, reads "General advice regarding the use and preservation of the eyes, ears, nose and throat." This describes its contents accurately. The advice given is simple, clear and good, so that the work should prove a help to the laity and also to nurses. We are brought up to take care of our teeth, but we have little instruction given us as to what to do in case of trouble of any of the organs of special sense, and it is well for the public to be instructed in such matters to the extent of Dr. Reik's brief but sufficiently comprehensive description.

*Pathfinders in Medicine.* By VICTOR ROBINSON. (New York: Medical Review of Reviews, 1912.)

The pathfinders selected are Galen, Aretaeus, Paracelsus, Ser-vetus, Vesalius, Paré, Scheele, Cavendish, Hunter, Jenner, Laennec, Simpson, Semmelweis, Schleiden and Schwann, and Darwin, the latter entitled by the author Saint of Science! We can conceive of no term which would have offended Darwin, the simplest of men, more than this. And this is but a sample of the florid and artificial style of the writer. Dr. A. Jacobi in a paragraph of his introduction to this book says that the author's facts are absolutely correct, and endorses the work as one that will instruct and edify its readers. This is no doubt true, but the student will find better studies elsewhere on almost all these pathfinders.

*London Medical Publications: Treatment After Operation.* By WILLIAM TURNER, F.R.C.S., etc., and C. ROCK CARLING, F.R.C.S., etc. (London: University of London Press, 1912.)

In a brief manner, which should make it most acceptable to the young student, the authors have described all the ordinary complications which may occur after any operation, including those on the eye—a chapter especially written for the book by



Dr. L. V. Cargill. The directions given are simple and reliable and the book is sufficiently and practically illustrated. Needless almost to add that some of the instruction is quite different from that commonly given in this country, but that ours is invariably right does not follow by any means; and it is well for us to study the opinions of others.

*Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India.* (Calcutta: Superintendent Government Printing, India, 1912.)

No. 54 (New Series). *Studies on the Mouth Parts and Sucking Apparatus in the Blood-Sucking Diptera.* No. 1. *Phlebotomyia Insignis* (Austen), by CAPTAIN F. W. CRAGG, M. D.

No. 55 (New Series). *The Structure of Hamaxotopota Plucialis* (Meigen), by CAPTAIN F. W. CRAGG, M. D.

No. 56 (New Series). *Malaria in the Andamans.* By MAJOR S. R. CHRISTOPHERS, M. B.

The first two reports are of such a technical character that they will interest but a few special workers. It is, however, well worth while to call attention to these "Scientific Memoirs" that students of biological problems may know where to find certain carefully prepared and well illustrated papers.

Major Christophers has prepared a brief report on Malaria in the Andamans, of value especially to the authorities there, in demonstrating the carrier of the disease, and the best means of preventing the spread of the infection among the convicts.

*International Clinics.* Vol. IV, Twenty-second Series. \$2. (Philadelphia and London: J. B. Lippincott Company, 1912.)

An article which will doubtless attract many readers in this volume is Auer's Description of the Rockefeller Institute. All intelligent physicians are interested from various points of view in this institution and it is fortunate that the *International Clinics* should have secured this paper. The proper method of tonsillectomy seems as yet unsettled, since Eves adds another to the many articles which have appeared in the last year on this subject. Weak feet, another quite modern surgical condition, is

considered by Steinhardt in a lucid, well illustrated paper. Indicating that primary principles are not generally understood, Bergonignan writes on The Features of the Normal Heart. While many of the remaining clinics are excellent, some of them seem too brief to deserve recording in these volumes.

*A Text-Book of General and Special Pathology for Students and Practitioners.* By HENRY T. BROOKS, M. D., formerly Professor of Pathology at the New York Post Graduate Medical School and Hospital, etc. \$8. (Philadelphia: F. A. Davis Company, 1912.)

In view of the numerous good, bad and indifferent books on Pathological Anatomy which have recently appeared, one wonders at the specific impulse which has led to the production of this volume. Dr. Brooks says in the preface that it was his original intention to prepare a translation of the third edition of "Grundriss der Pathologischen Anatomie," published in 1904 by Professor Robert Langerhans of Berlin. Unfortunately this idea was not carried out. Instead the author has felt it necessary to not only recast and greatly augment the subject matter to meet existing requirements, but to more fully adapt it to the needs of the undergraduate student and practitioner. The result is a new treatise presented as an independent work. This volume of more than 1700 pages of good paper is profusely illustrated by 525 half tones and other text engravings and 15 full page plates, etc., none of which can be considered to be brilliant. The heavy type and double spacing of letters so abundantly used are of questionable value and the use of Latin description, as has been done frequently by the author for the text figures, seems unfortunate.

The first paragraph of the book consists of a series of definitions which leave the reader somewhat confused after their perusal. The subjects are presented in the order usually found in text-books of pathology, but in many instances one can hardly feel that the author has taken advantage of the more recent advances in the subjects. Unfortunately these are not the greatest faults—these sins of omission—but the gross errors which are everywhere encountered throughout the book make it not only not valuable, but a dangerous book to put in the hands of anyone.

## BOOKS RECEIVED.

*A Treatise on Diseases of the Hair.* By George Thomas Jackson, M. D., and Charles Wood McMurtry, M. D. Illustrated with 109 engravings and 10 colored plates. 1912. 8vo. 366 pages. Lea and Febiger, Philadelphia and New York.

*Auto-Intoxication and Disintoxication.* An account of a New Fasting Treatment in Diabetes and other Chronic Diseases. By Dr. G. Guelpa (Paris). Translated by F. S. Arnold, B. A., M. B., B. Ch. (Oxon.). With an Introduction by the Translator and a Chapter on the Use of the Method in the Treatment of Morphine Addiction. By Oscar Jennings, M. D. (Paris). 1912. 12mo. 152 pages. Rebman Company, New York.

*Hypnosis and Suggestion.* Their Nature, Action, Importance and Position amongst Therapeutic Agents. By W. Hilger, M. D. Translated by R. W. Felkin, M. D., F. R. S. E. With an introduction by Dr. von Renterghem. Translated by A. Newbold. 1912. 8vo. 233 pages. Rebman Company, New York.

*International Clinics.* A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by Henry W. Cattell, A. M., M. D. Twenty-second Series. Volume III. 1912. 8vo. 306 pages. J. B. Lippincott Company, Philadelphia and London.

*Surgery of the Brain and Spinal Cord.* Based on Personal Experiments. By Prof. Fedor Krause, M. D. English adaptation by Dr. Max Thorex. Volume II. With 94 figures in the text, 14 of which are colored; 27 colored figures and four half-tone figures on fifteen plates. 1912. 4to. 819 pages. Vol. III. With 42 figures (three of which are colored) in the text, and 47 colored figures on 22 plates. 1912. 4to. 1201 pages. Rebman Company, New York.

*The Therapy of Syphilis.* Its Development and Present Position. By Dr. Paul Mulzer. With a preface by Prof. P. Uhlenhuth, M. D. Translated by A. Newbold. [1910.] 12mo. 247 pages. Rebman Company, New York.

*Pathology and Treatment of Diseases of Women.* Fourth edition, rewritten by A. Martin and Ph. Jung. Only Authorized English Translation, written and edited by Henry Schmitz, M. D. With one hundred and eighty-seven illustrations, twenty-five of which are in colors. 1912. 8vo. 475 pages. Rebman Company, New York.

*Transactions of the American Urological Association.* Eleventh Annual Meeting at New York City, April 2, 3 and 4, 1912. Edited by Charles Greene Cumston, M. D. 1912. 8vo. 439 pages. Riverdale Press, Brookline, Mass.

- Elementary Bacteriology and Protozoology.* The Microbiological Causes of the Infectious Diseases. By Herbert Fox, M.D. 1912. 12mo. 237 pages. Lea and Febiger, Philadelphia and New York.
- Further Researches into Induced Cell-Reproduction and Cancer.* Vol. II. Consisting of papers by H. C. Ross, M.R.C.S. Eng., L.R.C.P. Lond., J. W. Cropper, M.B., M.Sc. Liverpool, M.R.C.S. Eng., L.R.C.P. Lond., and E. H. Ross, M.R.C.S. Eng., L.R.C.P. Lond. With Illustrations. The McFadden Researches. 1912. 8vo. 125 pages. John Murray, London. P. Blakiston's Sons and Co., Philadelphia.
- The Wassermann Reaction. Its Technic and Practical Application in the Diagnosis of Syphilis.* By John W. Marchildon, B.S., M.D. Eleven Illustrations and Colored Frontispiece. 1912. 12mo. 103 pages. C. V. Mosby Company, St. Louis.
- The Principles and Practice of Medicine.* By Sir William Osler, Bt., M.D., F.R.S. Eighth edition, largely rewritten and thoroughly revised with the assistance of Thomas McCrae, M.D. 1912. 8vo. 1225 pages. D. Appleton and Company, New York.
- Obstetrics.* By J. Whitridge Williams. Third enlarged and revised edition. With sixteen plates and six hundred and sixty-eight illustrations in the text. 1912. 8vo. 977 pages. D. Appleton and Company, New York and London.
- The Blood: A Guide to Its Examination and to the Diagnosis and Treatment of Its Diseases.* By G. Lovell Gulland, M.A., B.Sc., M.D., F.R.C.P.E., and Alexander Goodall, M.D., F.R.C.P.E. With 16 text illustrations and 16 colored plates. E. B. Treat & Co., New York.
- The Kallikak Family. A Study in the Heredity of Feeble-Mindedness.* By Henry Herbert Goddard, Ph.D. 1912. 8vo. 121 pages. The Macmillan Company, New York.
- A Practical Text-Book of the Diseases of Women.* By Arthur H. N. Lewers, M.D. Lond., F.R.C.P. Lond. Seventh edition, with 258 illustrations, thirteen colored plates, five plates in black and white, and a large number of illustrative cases. 1912. 8vo. 540 pages. Paul B. Hoeber, New York.
- Life and Letters of Dr. William Beaumont.* Including Hitherto Unpublished Data Concerning the Case of Alexis St. Martin. By Jesse S. Myer, A.B., M.D. With an introduction by Sir William Osler, Bt., M.D., F.R.S. With fifty-eight illustrations. 1912. 8vo. 317 pages. C. V. Mosby Company, St. Louis.
- Symptoms And Their Interpretation.* By James MacKenzie, M.D., LL.D., Aber. and Edin. Second edition. 1912. 8vo. 304 pages. Paul B. Hoeber, New York.
- The Anatomy of the Human Eye. As Illustrated by Enlarged Stereoscopic Photographs.* By Arthur Thomson, M.A., M.B., F.R.C.S. 1912. 8vo. 61 pages. Clarendon Press, Oxford.
- Burdett's Hospital and Charities 1912.* Being the Year Book of Philanthropy and the Hospital Annual. By Sir Henry Burdett, K.C.B.K., C.V.O. The Scientific Press, London.
- Nervous and Mental Disease Monograph Series. No. 12. Cerebellar Functions.* By Dr. Andre-Thomas. Translated by W. Congers Herring, M.D., of New York. With 89 figures in the text. 1912. 8vo. 223 pages. The Journal of Nervous and Mental Disease Publishing Company, New York.
- Medical Symposium Series. No. 1. Recent Studies of Syphilis.* With Special Reference to Serodiagnosis and Treatment. Second edition (revised). A Reprint of Articles Published in the Interstate Medical Journal.
- Nervous and Mental Disease Monograph Series. No. 4. Selected Papers on Hysteria and Other Psychoneuroses.* By Prof. Sigmund Freud. (Second, Enlarged Edition.) Authorized Translation. By A. A. Brill, M.D., Ph. B. 1912. 8vo. 215 pages. The Journal of Nervous and Mental Disease Publishing Company, New York.
- Making Good on Private Duty.* Practical Hints to Graduate Nurses. By Harriet Camp Lounsbury, R.N. [1912.] 12mo. 208 pages. J. B. Lippincott Company, Philadelphia and London.
- Internal Medicine.* By David Bovaird, Jr., A.B., M.D. With 109 illustrations in the text and 7 colored plates. [1912.] 8vo. 618 pages. J. B. Lippincott Company, Philadelphia and London.
- Clinical Bacteriology and Hamatology.* By W. D'Este Emery, M.D., B.Sc. Lond. Fourth edition. 1912. 8vo. 274 pages. P. Blakiston's Son & Co., Philadelphia.
- Muscle Spasm and Degeneration in Intrathoracic Inflammations and Light Touch Palpation.* By Francis Marion Pottenger, A.M., M.D., LL.D. Sixteen illustrations. 1912. 8vo. 100 pages. C. V. Mosby Company, St. Louis.
- Brain and Spinal Cord: A Manual for the Study of the Morphology and Fibre-Tracts of the Central Nervous System.* By Dr. Med. Emil Villiger. Translated by George A. Piersol, M.D., Sc.D. From the Third German Edition with 232 illustrations. [1912.] 4to. 289 pages. J. B. Lippincott Company, Philadelphia and London.
- A Manual of Surgical Treatment.* By Sir W. Watson Cheyne, Bart., C.B., D.Sc., LL.D., F.R.C.S., F.R.S., and F. F. Burghard, M.S. (Lond.), F.R.C.S. New Edition. Entirely revised and largely rewritten with the assistance of T. P. Legg, M.S. (Lond.), F.R.C.S., and Arthur Edmunds, M.S. (Lond.), F.R.C.S. In Five Volumes. Vol. III. *The Treatment of the Surgical Affections of the Joints, the Spine, the Head, and the Face.* 1912. 8vo. 575 pages. Lea and Febiger, Philadelphia and New York.
- A Clinical Manual of The Malformations and Congenital Diseases of the Fetus.* By Professor Dr. R. Birnbaum. Translated and Annotated by G. Blacker, M.D., B.S., F.R.C.P., F.R.C.S. With 58 illustrations in the text and 8 plates. 1912. 8vo. 379 pages. P. Blakiston's Son & Co., Philadelphia.
- Manual of Human Embryology.* Written by Charles R. Bardeen, Herbert M. Evans, Walter Felix, Otto Grosser, Franz Keibel, Frederic T. Lewis, Warren H. Lewis, J. Playfair McMurrich, Franklin P. Mall, Charles S. Minot, Felix Pinkus, Florence R. Sabin, George L. Streeter, Julius Tandler, Emil Zuckerkandl. Edited by Franz Keibel and Franklin P. Mall. In two volumes. Volume II. With 658 illustrations. 1912. 4to. 1032 pages. J. B. Lippincott Company, Philadelphia and London.
- A Manual of Immunity.* By Elizabeth T. Fraser, M.D. (Glas.) 1912. 12mo. 199 pages. James Maclehose and Sons, Glasgow.
- Anesthetics and Their Administration.* By Sir Frederic W. Hewitt, M.V.O., M.A., M.D. Cantab. Fourth edition. Prepared with the assistance of Henry Robinson, M.A., M.D., B.C. Cantab. With illustrations. 1912. 8vo. 676 pages. Macmillan and Co., Limited, London.
- Diseases of the Liver, Gall-Bladder and Bile-Ducts.* By Humphry Davy Rolleston, M.A., M.D. (Cantab.), F.R.C.P. Illustrated. 1912. 8vo. 811 pages. Macmillan and Company, Limited, London.

- Ophthalmic Surgery. A Handbook of the Surgical Operations on the Eyeball and its Appendages as Practised at the Clinic of Hofrat Prof. Fuchs.* By Dr. Josef Meller. Edited by Dr. William M. Sweet. With 173 original illustrations. Second edition, thoroughly revised. 1912. 8vo. 289 pages. P. Blakiston's Son & Co., Philadelphia.
- Scientific Memoirs. New Series.* By Officers of the Medical and Sanitary Departments of the Government of India. Superintendent Government Printing, Calcutta, India.
- No. 51. *A Streptothrix Isolated from the Spleen of a Leper.* By Major W. G. Liston, M.D., D.P.H., I.M.S., and Captain T. S. B. Williams, I.M.S. 1912. 4to. 5 pages.
- No. 52. *Dysentery in Hazaribagh Central Jail, January, 1910-March 1911.* Being the Report of an Enquiry carried out by Captain R. T. Wells, M.A., M.B., I.M.S. 1912. 4to. 44 pages.
- No. 53. *The Development of the Parasite of Indian Kala Azar.* By Captain W. S. Patton, M.B., I.M.S. 1912. 4to. 38 pages.
- No. 54. *Studies on the Mouth Parts and Sucking Apparatus in the Blood-Sucking Diptera. No. 1. Philaematomyia Insignis.* Austen. By Captain F. W. Cragg, M.D., I.M.S. 1912. 4to. 17 pages.
- No. 55. *The Structure of Haematopota Pluvialis (Meigen).* By Captain F. W. Cragg, M.D., I.M.S. 1912. 4to. 36 pages.
- No. 56. *Malaria in the Andamans.* By Major S. R. Christophers, M.B., I.M.S. 1912. 4to. 48 pages.
- A Practical Medical Dictionary.* Of Words used in Medicine and Their Derivation and Pronunciation, Including Dental, Veterinary, Chemical Botanical, Electrical, Life Insurance and Other Special Terms [etc.]. By Thomas Lathrop Stedman, A.M., M.D. Second, revised edition. Illustrated. 1912. 8vo. 1016 pages. William Wood and Company, New York.
- St. Luke's Hospital.* Medical and Surgical Reports. Volume III. 1911. 8vo. 353 pages [1912.]. William G. Hewitt, Brooklyn, N. Y.
- Metropolitan Asylums Board.* Annual Report for the Year 1911. (14th year of issue.) 1912. 8vo. 258 pages. Ben Johnson & Co., London and York.
- Stuttering and Lipping.* By E. W. Scripture, Ph.D. (Leipzig), M.D. (Munich). 1912. 251 pages. The Macmillan Company, New York.
- Bacteria.* Dr. Max Schottelius. With 10 colored plates and 33 illustrations in the text. Second edition. Translated by Staff-Surgeon Herbert Geoghegan, R.N. 1912. 8vo. 324 pages. Henry Frowde, Hodder & Stoughton, London.
- Medical Inspection of Schools.* By Allen G. Rice, M.D., Fiske Fund Prize Dissertation. No. LV. 1912. 8vo. 109 pages. Snow & Farnham Company, Providence.
- The Psychology of Insanity.* By Bernard Hart, M.D. (Lond.). 1912. 16mo. 176 pages. University Press, Cambridge; G. P. Putnam's Sons, New York.
- The Chemic Problem in Nutrition (Magnesium Infiltration).* A Sketch of the Causative Factors in Disorders of Nutrition as Related to Diseases of the Nervous System. By John Aulde, M.D. Illustrated with four plates. 1912. 8vo. 410 pages. John Aulde, M.D., Philadelphia.
- A Practical Treatise on Fractures and Dislocations.* By Lewis A. Stimson, B.A., M.D., LL.D. (Yalen). Seventh edition, revised and enlarged. With 459 illustrations and 39 plates in monotyp. 1912. 8vo. 930 pages. Lea & Febiger, New York and Philadelphia.
- Diseases of the Stomach, Intestines, and Pancreas.* By Robert Coleman Kemp, M.D. With 388 illustrations, some in colors. Second edition, revised and enlarged. 1912. 8vo. 1021 pages. W. B. Saunders Company, Philadelphia and London.
- A Text-Book Upon the Pathogenic Bacteria and Protozoa.* By Joseph McFarland, M.D. With 293 illustrations, a number of them in colors. Seventh edition, thoroughly revised. 1912. 8vo. 878 pages. W. B. Saunders Company, Philadelphia and London.
- An Introduction to the Study of Infection and Immunity.* Including Chapters on Serum Therapy, Vaccine Therapy, Chemotherapy, and Serum Diagnosis. By Charles E. Simon, B.A., M.D. Illustrated. 1912. 8vo. 301 pages. Lea & Febiger, Philadelphia and New York.
- Guide to Midwifery.* By David Berry Hart, M.D., F.R.C.P.E. With 4 illustrations in color and 268 diagrams. 1912. 8vo. 765 pages. Rebman Company, New York.
- Practical Physiological Chemistry.* A Book Designed for Use in Courses in Practical Physiological Chemistry in Schools of Medicine and of Science. By Philip B. Hawk, M.S., Ph.D. Fourth edition, revised and enlarged. With 2 full-page plates of absorption spectra in colors, four additional full-page color plates and 137 figures of which 12 are in colors. 1912. 8vo. 475 pages. P. Blakiston's Son Co., Philadelphia.
- The Principles of Hygiene.* A Practical Manual for Students, Physicians, and Health Officers. By D. H. Bergey, A.M., M.D. Illustrated. Fourth edition, thoroughly revised. 1912. 8vo. 529 pages. W. B. Saunders Company, Philadelphia and London.
- New Aspects of Diabetes.* Pathology and Treatment. By Prof. Dr. Carl von Noorden. Lectures delivered at the New York Post-Graduate Medical School, New York. 1912. 12mo. 160 pages. E. B. Treat & Company, New York.
- A Treatise on Pellagra.* By Edward Jenner Wood, S.B., M.D. With 38 illustrations in text. 1912. 8vo. 377 pages. D. Appleton and Company, New York and London.
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- Text-Book of Anatomy and Physiology.* For Nurses. By Elizabeth R. Bundy, M.D. Second edition revised and enlarged. With a glossary and 215 illustrations 42 of which are printed in colors. 1913. 8vo. 335 pages. P. Blakiston's Son & Co., Philadelphia.



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*Transactions of the American Association of Genito-Urinary Surgeons.* Twenty-sixth annual meeting held at Philadelphia, June 7 and 8, 1912. Vol. VII. 1912. 8vo. 315 pages. Published for the Association by Frederick H. Hitchcock, New York.

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*Michigan State Board of Health.* Thirty-ninth Annual Report of the Secretary of the State Board of Health of the State of Michigan for the fiscal year ending June 30, 1911. By Authority. 1912. 8vo. 118 pages. Lansing, Michigan.

*United States Treasury Department Public Health and Marine Hospital Service.* Public Health Reports. Issued in weekly numbers by the United States Public Health Service. Volume XXVII, Part I. Numbers 1-26. January-June, 1912. 1912. 8vo. 1066 pages. Government Printing Office, Washington.

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*Association of American Physicians.* Transactions. Twenty-seventh session, May 14 and 15, 1912. Volume XXVII. 1912. 8vo. 668 pages. Printed for the Association, Philadelphia.

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Thursdays, 10 to 12 m.

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Bacteriology.	Anesthesia.
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Serum Diagnosis.	Gynecological Cystoscopy.
Diseases of Circulation.	Gynecological Dispensary.
Digestive Diseases.	Pediatrics.
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with Ward Rounds.	Genito-Urinary Surgery (b).
Surgical Operations.	

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Courses cannot be changed after registration, except upon the payment of an additional fee.

In view of the fact that only a limited number can be admitted to some of the courses, it is advisable that applications be made in advance. Address the Dean of the Johns Hopkins Medical School, Baltimore.

# BULLETIN

OF

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## THE EVOLUTION OF THE THYROID GLAND.

By DAVID MARINE, M. D.

(From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University,<sup>1</sup> Cleveland.)

The thyroid while it does not play an essential rôle in our conception of vertebrates is, nevertheless, one of their most constant and characteristic structures—existing in the same anatomical form from the adult cyclostomes (Petromyzon and Bdellostoma) throughout all the fishes, amphibians, reptiles, birds and mammals.

In the larval Petromyzon—Ammocetes branchialis—in Amphioxus and in all Tunicates there exists in the ventral midline of the branchial sac a gland-like structure which Huxley<sup>2</sup> first designated as "Endostyle." This endostyle or

better, endostylar mechanism<sup>3</sup> has, through the work of Goodrich, been shown to have the same general structure in both the Tunicates and Amphioxus, and Wilhelm Müller (Jenaische Zeitschrift, 1873, VII, 327), in 1873, pointed out the similarity of the structure in Ammocetes with that of the Tunicates and Amphioxus and suggested that the endostyle of the lower chordates was homologous with the ductless thyroid of the higher chordates. This homology has been strengthened by the subsequent work of Anton Schneider (Thyroidea von Ammocetes, Beiträge z. Vergleich. Anat. u. Entwcklungs-

introduced and is now quite generally applied to the endostyle of Ammocetes. Inasmuch as it has no resemblance to a true thyroid and is entirely similar to the endostyle of the Tunicates and Amphioxus I will use the term "Thyroid" only in connection with the ductless follicle formations.

<sup>3</sup>In Tunicates in addition to the glandular portion of the endostyle or hypobranchial groove there are two anterior peripharyngeal ciliated bands which begin at the anterior end of the glandular portion of the endostyle, arch around the anterior end of the branchial sac—one on each side—to join in the dorsal midline in the ciliated dorsal ridge or lamina which extends directly posterior to the entrance into the œsophagus. At the posterior end of the hypobranchial groove the marginal folds form two slight ridges which have been traced around the posterior end of the branchial sac to join the dorsal lamina near its termination in the œsophagus.

In Amphioxus the two peripharyngeal grooves also start from the anterior termination of the glandular portion of the endostyle and arch around the anterior border of the branchial sac to meet

<sup>1</sup>The observations on the Tunicates and Amphioxus were made at the Marine Biological Station at San Diego during the summer of 1911. I am indebted to Dr. W. E. Ritter, Director, for the privileges and excellent facilities of his laboratory. The work with Ammocetes was done in the Laboratory of Histology and Embryology, of Cornell University, during the summer of 1912. I wish to thank Dr. B. F. Kingsbury for the privileges of his laboratory and many helpful suggestions and criticisms.

<sup>2</sup>Huxley (Observations on Salpa, Pyrosoma, Doliolum, etc., Philos. Trans., 1851, 566) appears to have first introduced the term "Endostyle." He so named it from his belief that this prominent fold in the Tunicates branchial sac was rod-like and served as a brace for the delicate branchial sac. Later work showed it to be a groove lined with highly differentiated gland cells. In German literature it is usually spoken of as the "Hypobranchial Groove." At present both terms are in common use for the structure in both the Tunicates and Amphioxus. When a similar structure in Ammocetes was found to give rise to the ductless thyroid follicles at metamorphosis the term "Thyroid" was



gesell. der Wirbelthiere. Berlin, 1879, 85) and Anton Dohrn (Die Thyroidea bei Petromyzon, Amphioxus und den Tunikaten, Mittheil. Zool. Stat., Neapel, 1886, VI, 49) and is as firmly founded as morphological studies make possible. Below the chordates nothing comparable to an endostylar structure has been made out and even in the lowest class of chordates—*Balanoglossus*—the structure is absent. Ritter (On a new *Balanoglossus* larva from the coast of California and its possession of an endostyle, Zool. Anz., 1894, XVII, 24) has described a ridge or band of high ciliated epithelium in the midline of the oesophagus of a *Tornaria* (larval *Balanoglossus*) which, from its location and from the generally accepted systemic position of *Balanoglossus* he suggested might be homologous with the Tunicates endostyle. Morgan (The Development of *Balanoglossus*, Jour. of Morph., 1894, IX, 1) also described this structure but did not use it as evidence of this animal's possible relation to the true chordates. While I was working in Dr. Ritter's laboratory during the summer of 1911 the question of the relation of this oro-oesophageal mechanism of *Tornaria* to the Tunicate endostyle was discussed with him and he expressed the opinion that the evidence was insufficient for assuming any phylogenetic relationship.

Leaving out *Balanoglossus* as doubtful possibly as regards its systemic position as a chordate and certainly as regards the endostylar nature of the oro-oesophageal, ciliated, gland cell mechanism, the lowest undoubted and living relative of the thyroid mechanism is found in the Tunicates.\*

More than a thousand species of Tunicates have been described (Ritter, W. E.: Am. Naturalist, 1907, XLI, 453). The several groups present great variations in external appearance (sessile, pelagic, simple, colonial) although their internal structure is strikingly constant. The endostylar mechanism is a good example of this constancy of organs and it rarely presents variations in morphology sufficient to be of value in the differentiation of species (Herdman: Liverpool Marine Biol. Mem., 1899, XI, No. 1, 14).

The large simple Ascidian *Holocynthia johnsonii*, is very common in San Diego Bay and most of my observations were

in the dorsal midline in the dorsal groove (a ridge in Tunicates) which extends back to the entrance to the oesophagus.

In *Ammocoetes* the grooves are more prominent owing to the fact that the glandular portion of the endostyle is largely cut off from the pharynx and opens into it by a large duct-like elliptical opening. Beginning at the anterior lip of this duct and continuous with it is a correspondingly large, deep, ciliated groove (T-shaped in cross-section) which after extending a short distance anteriorly branches into right and left ciliated peripharyngeal grooves which arch around the anterior end of the pharynx to join the prominent midline dorsal ridge where they fuse with the ciliated epithelium on the sides of this pendant-like fold and continue back to the oesophagus. The ventral or most dependent portion of this fold is covered with stratified squamous epithelium out of which the permanent oesophagus will be formed. Beginning at the posterior lip of the endostyle duct and continuous with it is a midline, shallow, ciliated groove which extends back to the entrance to the larval oesophagus.

\*The endostyle-thyroid mechanism has been utilized in the philosophical discussions of the origin of vertebrates. Whether

made on this species, although through the courtesy of Dr. Ritter I made microscopic preparations from many of his general collection of Tunicates including several species of *Salpa*, *Pyrosoma*, *Ciona*, *Cynthia*, *Doliolum* and *Appendicularia*.

#### TUNICATES.

(FIG. 1, PLATE III, AND FIG. 2.)

The glandular portion of the endostylar mechanism forms a groove (roughly U-shaped in cross-section) lying in the ventral midline of the pharyngeal or branchial sac. This groove begins near the anterior end of the pharynx just posterior to the oral tentacles, at the ventral junction of the peripharyngeal ciliated bands and extends backward nearly to the oesophagus. In all the larger Tunicates it is visible to the naked eye as a prominent, whitish, longitudinal fold embedded in the wall of the branchial sac. The groove opens throughout its length into the branchial sac but owing to the elasticity of the branchial sac and the muscular mantle the mechanism exists for closing the groove by apposing its lateral walls.

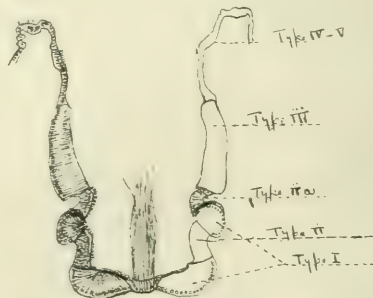


FIG. 2.—Diagrammatic outline of endostyle of *Holocynthia johnsonii* as seen in cross-section.

Histologically the groove is lined with highly differentiated gland cells. When seen in cross-section there is in the ventral midline of the groove a tract composed of closely packed columnar cells with deeply staining nuclei bearing whiplike cilia whose lengths in many species nearly equal the depth of the groove. On either side of this unpaired tract of ciliated

the primitive Tunicate which Brooks (The Genus *Salpa*—Johns Hopkins Press, Baltimore, 1893) believed was typified in all essentials in the existing *Appendicularia* arose in the main stem of the descent of chordates or whether all Tunicates are degenerate forms of fish-like ancestors unrelated to the vertebrate tree, as Dohrn and others believe, is a question that does not concern us here. The data of the endostyle-thyroid mechanism can only be a minor item in such a controversy, but so far as they can be utilized in the elaboration of any hypothesis of the origin of vertebrates it seems that the views of Brooks more nearly harmonize these facts of structure, function and historical sequence than do the views of Dohrn, Gaskell, Patten and others which would leave the origin of the endostyle unexplained. Brooks (Origin of the Thyroid, Johns Hopkins Hosp. Bull., 1893, IV, 47) considered the endostyle of the Tunicate to have arisen with the branchial sac as a specialization to meet the needs of its habits and modes of life.

cells the fundus, lateral wall and marginal fold of the groove contain symmetrical epithelial formations. These symmetrical epithelial tracts form the basis of homology with the endostyle of *Amphioxus* and *Ammocetes*. There are at least four and possibly five types of epithelia. The most uniformly constant type in form and position comprises two large tracts of cuneiform gland cells in each half of the endostyle which I will call Type I. These wedge-shaped cells of each tract are arranged radially from the common point of opening into the endostylar groove and each bundle is roughly fan-shaped. The more ventral bundle is usually slightly larger. The cells are pale, granular, with large vesicular nuclei lying at the bases of the cells (periphery of the bundle). These two bundles of Type I cells in each half are separated by an intervening layer of short, closely packed, columnar, ciliated cells with deeply staining nuclei lying in different levels of the cell bodies which may be designated as Type II. The height and extent of these cells vary with different species being as a rule more extensive in the *Salpae*. Just above the upper bundles of cuneiform cells (Type I) and closely applied to them is another short area of cells, columnar and ciliated in *Ascidians* and cuboidal in *Salpae*, which differ from the cells of Type II. For convenience these may be spoken of as Type II-A. Above this somewhat variable layer of Type II-A cells is a very long area in each half of large, high, columnar cells that may be designated as Type III. These cells are not ciliated in any of the species examined. Above this group in each half and continuing to the marginal fold or lips of the groove is another group which I shall designate as Types IV and V. These cells are in general cuboidal, often containing yellow pigment granules, and non-ciliated although, just at the margin of the fold and its junction with the branchial mucosa, there is on each side a small area of ciliated, low, columnar cells with deeply staining nuclei.

Summing up then, the endostylar groove proper is lined with highly differentiated epithelium which may be divided into at least four and possibly five different types in addition to the unpaired midline epithelium.

#### AMPHIOXUS LANCEOLATUS.

(FIG. 3, PLATE III, AND FIG. 4.)

The glandular portion of the endostyle in the adult *Amphioxus* forms a broad shallow groove situated in the ventral

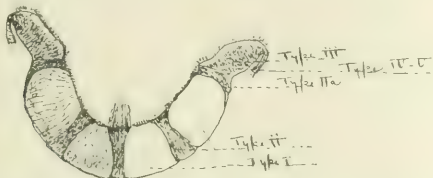


FIG. 4.—Diagrammatic outline of cross-section of endostyle of *Amphioxus calif.*

midline of the pharynx and extending practically the whole length of the pharynx terminating anteriorly in the peri-

pharyngeal ciliated bands and posteriorly just anterior to the cesophagus. The groove opens into the branchial sac throughout its length and it does not appear that the groove can be closed off from the pharynx as it can be in the *Tunicates*.

Histologically as Goodsir, Müller, Schneider, Dohrn and many others have shown it is composed of the same basic types of epithelium already described for the *Tunicates*. Seen in cross-section there is in the ventral midline of the endostyle a small bundle of tall, columnar, deeply staining cells with long upright cilia. On either side of this unpaired tract are two bundles of large, pale, columnar, slightly wedge-shaped cells, which, on account of their resemblance to Type I of the *Tunicates*, may also be designated as Type I. They differ from the corresponding cells of the *Tunicates* in that they are tipped with short cilia-like processes. Between the two bundles of cells of Type I on either side is a very narrow layer of columnar ciliated cells with deeply staining nuclei which from their location and staining characteristics are similar to Type II of the *Tunicates* and may here be designated as Type II. Just above and closely applied to the upper bundle of cuneiform cells of Type I on each side is a very narrow zone of cells which, as regards size, shape and staining reaction, are almost identical with Type II and I have designated them Type II-A since they correspond in position to the group of cells designated Type II-A for the *Tunicates*. Beyond or above the cells of Type II-A and producing the marginal fold are long areas of high columnar, ciliated, closely packed cells with deeply staining nuclei which, as regards extent and location, closely resemble the Type III for the *Tunicate* endostyle except that they are ciliated and may also be designated as Type III for the *Amphioxus*. Above the cells of Type III and curving sharply externally and ventrally and fusing with the branchial mucosa in the ventral-lateral sulcus of the pharynx is a poorly defined layer of low cuboidal epithelium which is analogous with Types IV and V of the *Tunicates* in position and structure and may also be designated Types IV and V.

To sum up then, the endostylar groove proper is lined by highly differentiated epithelia of at least four different types in addition to the median, unpaired, ciliated tract and is similar in all its general characteristics to the endostyle of *Tunicates*. There are some differences. Thus the groove in *Amphioxus* is more compact, shallower and relatively wider than in *Tunicates*. Only three of the types of epithelium are contained in the groove proper in *Amphioxus* and all these cells are ciliated and of quite uniform height. These differences are but modifications as the fundamental structures correspond with those of the *Tunicates*.

#### AMMOCTES BRANCHIALIS.

(FIGS. 5 AND 6, PLATE III.)

The fully developed endostylar groove shows many modifications of the form seen in the *Tunicates* and *Amphioxus*. Thus the glandular portion is shut off from the pharynx except for the large elliptical duct-like orifice, and the pharyngeal grooves anteriorly and posteriorly are correspondingly

increased. Embryologically it has been shown (Reese, A. M.: Proc. Am. Acad. Nat. Sci., Phila., 1902, 85) that at first the endostyle is an open ventral midline groove in the floor of the branchial sac just as in Tunicates and Amphioxus but in the course of its development great distortions and modifications are required.

The glandular portion of the endostyle is divided into symmetrical right and left halves by the median septum and each half contains the same complement of epithelia that is present in the whole endostyle of the Tunicates or Amphioxus, or in other words—the fully developed endostyle of *Ammocoetes* is similar to two simple endostyles placed side by side. In cross-section of a half of the endostyle one notes the absence of the tract of cells which in Tunicates and Amphioxus bears the long whiplike cilia as well as of any tract of cells that may be homologized with them. The next group of cells consists of the four tracts—two on each side of the midline of each half—of large cuneiform cells which in shape, size and staining reactions are identical with Type I of the Amphioxus and Tunicate endostyle. These cells formed the basis for the first homology by Müller. On each side of the openings of these bundles of wedge-shaped cells are areas of columnar, ciliated, closely set cells with deeply staining nuclei that may be designated as Type II since they correspond in location and type to the Type II of Amphioxus and Tunicates. Closely applied to one border of the cells of Type II is another group of larger, columnar, ciliated cells with large vesicular nuclei and containing yellow pigment granules which I have designated Type III. In the Tunicate endostyle the yellow pigment is commonly present in the cells which have been grouped under Types IV and V. It may be, therefore, that the epithelium grouped as Type III in the *Ammocoetes* endostyle is actually homologous with Types IV and V of Tunicates rather than with the epithelium I have grouped as Type III. Beyond Type III, covering the apex of the visceral invagination and the baso-lateral angles and continuous with the epithelium lining the duct and pharyngeal groove, is another type which in *Ammocoetes* I have grouped separately as Type IV. As will be seen later this Type IV is the most important epithelium concerned in the formation of the ductless thyroid follicles at metamorphosis. Type IV merges into another form which lines the parietal wall of the chamber and is designated as Type V. The cells of this type are flat, almost endothelial in form.

The metamorphosis (Fig. 7, Plate III) of *Ammocoetes* into *Petromyzon* which was first made known in 1856 by A. Müller gives us the great connecting link in the evolution of the thyroid mechanism, without which the relation of the endostyle to the thyroid could not have been known. The occurrence of a living animal which in its larval form has an endostyle only and in its adult form a ductless thyroid only allows one to observe the formation of typical ductless thyroid follicles out of the fullest development of the endostyle. Only the endostyle of larval Cyclostomes undergoes this metamorphosis. The metamorphosis from its beginning to its completion in *Ammocoetes* extends over a period of at least a month. The

endostylar changes are at first a general shrinkage in all the component parts of the organ. The changes of greatest significance are those of the epithelia. The first to disappear are the tracts of large cuneiform cells (Type I) which are the most characteristic cell groups in the endostyle. The cells of Type III stand next to those of Type I in point of the rapidity of the cell atrophy and absorption although remnants of this type (easily identified by means of the yellow pigment) can be seen after the ductless follicles are formed. The flattened epithelial cells of Type V show the next most extensive changes although here also atrophic and distorted cell masses may be preserved until ductless follicle formation is nearing completion. It seems certain that the cells of Types I, III and V take no part in the ductless follicle formation. With the Types II and IV one cannot be certain that both do not take part although Type IV is certainly the most important epithelium persisting as the lining epithelium of the permanent follicles. The fact that Type IV is the predominant persistent epithelium of the ductless follicles and also that it is continuous with and probably identical with that epithelium lining the gland duct and the ventral pharyngeal grooves seems to me of the greatest significance in the interpretation of the origin of the thyroid of higher vertebrates. This observation, taken in connection with the observations of Dohrn that in the torpedo embryo transient rudimentary pharyngeal grooves are present, is strong evidence that the ductless thyroid of higher vertebrates originates from a pharyngeal anlage closely related to if not homologous with the epithelium which lines the pharyngeal groove and duct of the *Ammocoetes* endostyle.

The ductless thyroid follicle of the type present in *Petromyzon* persists throughout all the remaining classes of vertebrates in the same anatomical form and this allows some conception of the vast antiquity of the gland. In none of the chordates above the larval Cyclostomes is there a true endostyle formation. Dohrn and others have shown that a transient and rudimentary formation of the pharyngeal grooves can be made out in the very early stages of development of the lower rays and sharks but even this remnant of the endostylar mechanism cannot be traced into the higher vertebrates.

Beginning with the fishes and continuing throughout the remaining vertebrates the problem of the evolution of the thyroid is the problem of the embryology, which is still unsettled as regards mammals. In fishes the thyroid resembles very closely that of *Petromyzon* in position, arrangement of follicles, and as a rule (excepting elasmobranchii) in the absence of a capsule. The gland in fishes arises from a single median ventral anlage of entoderm in the region of the first gill arch.

In amphibians the adult thyroid is paired. Each body is surrounded by a fibrous capsule. Embryologically the gland arises from a single median ventral anlage of entoderm in the region of the first gill arch. This anlage grows downward and backward and divides into right and left halves which in the adult frog come to lie on the ventral surface of the posterior horns of the hyoid bones (Mayer: Zur Lehre von der



Schilddrüse und Thymus bei den Amphibien. *Anat. Anz.*, 1888, III, 97).

In reptiles the adult thyroid is unpaired in the snakes (ophidia) and turtles (chelonia) and paired in the other groups (lizards, crocodiles, etc.) and lies in the thoracic cavity just above the pericardium. Embryologically all observers are in agreement that it arises from a single median ventral anlage in the region of the first gill arch and is shifted backward with the aortic arteries.

In birds the thyroid lobes are separate, oval bodies placed on each side of the vertebral column a short distance above the pericardium and usually partially imbedded in the lower-most lobules of the thymus. Embryologically the first accurate description was given by Remak in 1855 who derived the gland from an unpaired median ventral anlage of pharyngeal endoderm in the region of the first gill arch. He observed that as development proceeded it divided into a T-shaped process and shifted backward with the aortic arches to occupy an intra-thoracic position. The thyreo-glossal tract and isthmus were absorbed. These observations were accepted (by Gotte, Müller and Seessel) until 1881 when Stieda and Wölfler stated that the thyroid had a lateral origin as well as a median. Mall, in 1887 (*Archiv. f. Anat. u. Physiol.*, 1887, 1-34), working with the development of the chick thyroid came to the conclusion of Remak that the chick thyroid is derived wholly from the single median anlage in the region of the first gill arch. The derivatives of the fourth gill pouch Mall designated as "Körpern Y" and concluded that they had nothing to do with the thyroid. Subsequent work has established the original views of Remak, Müller and Mall, that the avian thyroid is derived solely from the single, median, ventral, pharyngeal anlage of the first aortic arch.

In mammals the question as to whether the thyroid arises from one or three anlagen is still argued although the evidence brought forward during the last ten years has apparently settled the controversy. In mammals only, therefore, is there at present any doubt as to the single and median origin of the thyroid. Many of the earlier observers including Wilhelm Müller (*Jenaische Zeitschrift*, 1871, VI, 428) believed the mammalian thyroid arose from the single median anlage. Although Remak in the chick, His and Kölliker in the rabbit, Wölfler and others had partially observed paired lateral bodies whose fate could not be decided but which some believed to be part of the thyroid tissue, it remained for Stieda, in 1881, working with sheep embryos, to give the first important description of these paired bodies from the fourth pouch and he called them "Lateral thyroid anlagen." He believed the whole thyroid was derived from these two lateral anlagen. In 1883 Born (*Archiv. f. mikr. Anat.*, 1883, XXII, 271), working with pig embryos confirmed Stieda's discovery of the lateral thyroid anlagen, but showed that the median anlage formed thyroid tissue and fused with the two lateral anlagen thus deriving the thyroid from three separate anlagen. His in 1885 (*Anatomie menschlicher Embryonen*, Leipzig, 1885, Heft 3), working with human embryos also found these lateral thyroid anlagen arising from the fourth pouch and

concluded that the median anlage formed the isthmus and pyramidal process of the thyroid while the lateral anlagen formed the lateral lobes. This view, while it prevailed for 20 years following 1885, was questioned by Kastschenko, in 1887 (*Archiv. f. mikr. Anat.*, 1887, XXX, 1), who worked with the sheep embryo. He concluded that these lateral anlagen played no important rôle in the development of the thyroid. These same bodies in the chick Mall had designated "Körpern Y." Van Bemmelen, in 1889 (*Anat. Anz.*, 1889, IV, 400), homologized the "Körpern Y" (Mall) of chicks, post-branchial bodies (Maurer) of amphibians and the lateral thyroid anlagen (Stieda, Born) of mammals with the superpericardial bodies (Van Bemmelen) of Selachians and Ganoids. The later work of Maurer (*Die Schlundspaltenderivative von Echidna*, Verhandl. d. Anat. Gesellsch., 1899, XIII, 88) of Hermann and Verdun (*Compt. rend. Soc. Biol.*, 1900, LII, 933) have further established that the lateral thyroid anlagen or post-branchial bodies play no part in the development of the thyroid, that in the lower mammals (Monotremes and

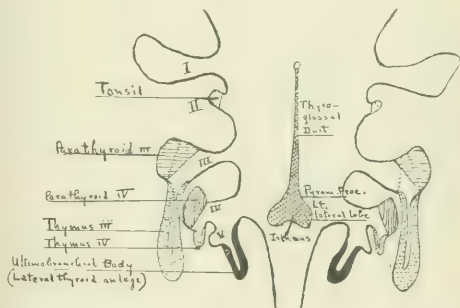


FIG. 8.—Schema of the branchiogenic derivatives in man (after Grosser in Kelbel and Mall—Human Embryology, 1912, II, 461).

Marsupials) they tend to remain separate from the thyroid proper, although in the placental mammals they are as a rule imbedded in the posterior lateral portion of the lateral thyroid lobes. Fox (*Am. Jour. Anat.*, 1908, VIII, 187) arrived at similar conclusions for the rabbit embryo. Grosser (*Anat. Anz.*, 1910, XXXVII, 337) has summarized this trend in the views as to the fate of the lateral thyroid anlagen. He would abandon the term "Lateral Thyroid Anlagen" as a misnomer and would substitute the terms "Ultimobranchial" or "Telo-branchial" body instead of post-branchial body (Maurer) or superpericardial body (Van Bemmelen) because it is believed that in the human embryo these bodies are derived from the rudimentary fifth pouch rather than from the fourth. (Fig. 8.)

With this short review of the embryological evidence that the mammalian thyroid is derived wholly from the median anlage I shall next review briefly the equally important evidence obtained from the developmental anomalies and the pathology all of which is associated with the median anlage. It has long been known that thyroid tissue in the form of a tract or as isolated masses was not of uncommon occurrence

along the path of descent of the original thyroid anlage, i. e. from the foramen cæcum to the thyroid isthmus (Merten: Archiv f. Anat. u. Physiol., Anat. Abth., 1879, 483). Streck-eisen (Virchow's Archiv, 1886, CIII, 131 and 215), in a careful series of observations on the human thyroid, showed that the persistence of thyroid tissue along the thyreo-glossal tract was very common in districts where goitre was endemic and was always associated with a general thyroid enlargement which probably began during fetal life. His (Archiv f. Anat. u. Physiol., Anat. Abth., 1891, 26) pointed out that in man the thyroid tract begins to atrophy normally during the fifth week of intra-uterine life. When abnormal demands for thyroid activity begin before this normal atrophy is completed a cell proliferation involving all the existing thyroid tissue takes place instead of the physiological resorption. The so-called sub-lingual, suprahyoid and infrahyoid thyroid masses as well as the pyramidal process are the commoner persistent forms of the thyreo-glossal tract. Thyreo-glossal cysts in which all thyroid tissue have disappeared are also relatively common in goitre districts. While much less studied, similar evidences of persistent remnants of the thyreo-glossal tract are present in the lower mammals. Wölfler has described such cases. I have also seen many instances in congenital goitre in dogs. Here the most common forms are the subhyoid accessory thyroids and the persistence of the thyroid isthmus. Goodey (Anat. Anz., 1910, XXXVI, 104) has described a persistent canal of His (thyreo-glossal duct) in a primitive selachian (*Chlamydoselachus Anguineus*).

In cases of aplasia of the thyroid Marech (Zeitschr. f. Heilkunde, 1898, XIX, 249) and Erdheim (Zeigler's Beitr. z. Path. Anat. u. Allg. Path., 1904, XXXV, 366) have shown that the parathyroids are usually normal but that in the region of the fourth pouch parathyroid a cystic endotermal rest corresponding to the post-branchial or ultimo-branchial body or lateral thyroid anlage may usually be found although never any thyroid tissue. Getsowa (Virchow's Archiv, 1911, CCV, 208) working with the atrophic goitrous thyroids of cretins and idiots has observed these cell rests and cysts between the fourth pouch parathyroid and the lateral thyroid lobes. She noted that these rests did not react with the thyroid in developing goitre and considered them as ultimo-branchial bodies, which in mammals are functionless remnants or at least take no part in the formation of thyroid tissue.

All the evidence, therefore, from embryology, from congenital developmental defects, and from pathology is against the view that the post-branchial bodies or "Körpern Y" or lateral thyroid anlagen have any part in the formation of the thyroid gland. The different conclusions of the earlier observers were probably due in part at least to the fact that in mammals these bodies fused with the lateral thyroid lobes although in all lower vertebrates they remained separate and while functionless in mammals are believed to be active organs in sharks and possibly amphibians.

#### PHYSIOLOGY.

Concerning the function of the endostyle organ little is known. The observations and experiments of Giard (Arch.

de Zool. Exper., 1873, I, 525 and 1873, II) and Fol (Morph. Jahrb., 1874, I, 222) on the transparent *Synascidia*, *Salpa* and *Doliolum* by means of India ink have shown that the endostyle is an active gland concerned in an important way with the collection of and possibly digestion of food. They observed that the gland cells secrete a slime or mucinous substance in which the food particles taken into the branchial sac with the respired water are caught up and that this mucin is formed into a cord by means of the cilia and carried forward to the peripharyngeal bands, thence along these ciliated tracts to the dorsal lamina and thence backward to the œsophagus. These observations have been confirmed by subsequent observers. All observers have suggested a possible chemical digestive action for this mucin but of this possibility nothing is known.

Reasoning from analogy the same function is believed to obtain in the *Amphioxus* and *Ammocetes* endostyles. Alcock (Jour. Anat. and Physiol., 1899, XXXIII, 612), working under Gaskell, studied the digestive effects of extracts of various *Ammocetes* tissues on fibrin. She was able to demonstrate a pepsin-like ferment in the liver, intestine and pharynx, but could obtain no evidence that the endostyle contained any proteolytic ferment.

In view of the important relation of iodine to the ductless thyroid I have made several iodine determinations on the tissues of *Holocynthia johnsonii*, on *Salpa confederata* and *Amphioxus* the averages of which are as follows:

	Mgms. of iodine per Gm. dried tissue.
<i>Salpa confederata</i> (whole animal).....	Trace
<i>Holocynthia johnsonii</i> (whole animal except tunic).....	0.03
" " tunic tissue .....	3.63
" " branchial sac tissue.....	0.00
" " endostyle tissue .....	0.00
" " dorsal lamina tissue .....	0.00
" " mantle (muscular tissue).....	0.01
" " gut (with contents).....	0.08
" " liver tissue .....	0.03
" " ova .....	0.01
<i>Octopus</i> —legs .....	0.00
<i>Amphioxus lanceolatus</i> (whole animal).....	Trace

The results are wholly negative as regards the endostyle but one thing of interest, which so far as I have seen is not referred to, is the very high iodine content of the tunic of the Ascidians. The tunic contains much cellulose and the presence of iodine in it may be of the same significance as in ocean plant life generally.

As to *Ammocetes*, I have kept them for nine months in an atmosphere of iodine to see whether the structure of the endostyle might be modified by it. The results were entirely negative. Iodine determinations were not made on the endostyle tissue either with or without administration of iodine. From these meager observations on the physiology of the endostyle one can state only what morphologists had already stated, that the function of the endostyle is probably quite different from that of the ductless thyroid. From its size and position at the beginning of the alimentary tract of all the three classes of animals possessing the endostyle and from its known mechanical action in the collection of food particles by

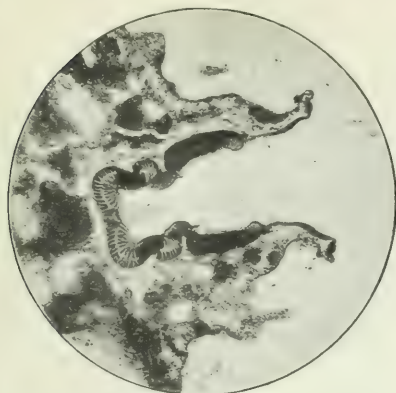


FIG. 1. Photomicrograph of cross-section of endostyle of *Holocynthia johnsonii* with adjacent parts of branchial sac.



FIG. 2.—Photomicrograph of cross-section of endostyle of *Amphioxus calif.*, showing relation to branchial sac and gill filaments.



FIG. 5.—Photomicrograph of endostyle of *Ammocetes branchialis* as seen in cross-section at the level of the duct. One notes twice the epithelial complement of the simple endostyle of *Amphioxus* or *Tunicates*.

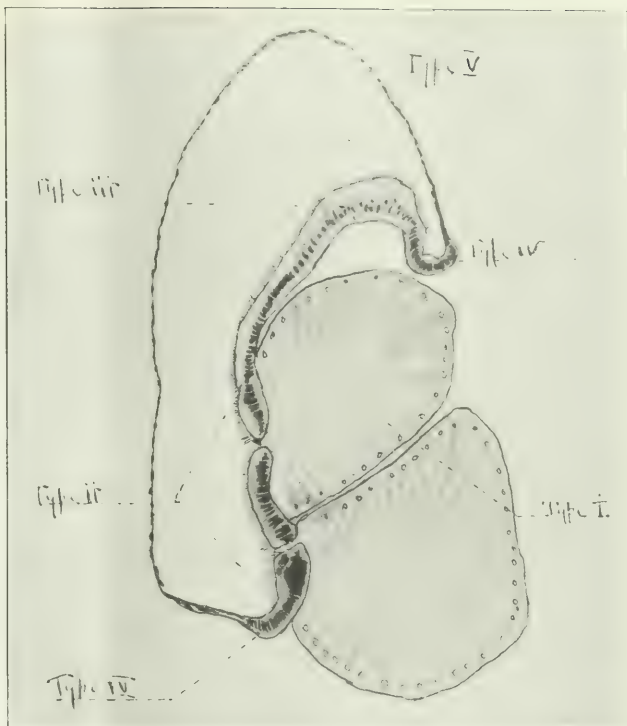


FIG. 6.—Camera outline of cross-section of the left external chamber of the endostyle of *Ammocetes* posterior to the coiled inner chambers, i. e., containing  $\frac{1}{4}$  the epithelial investment of the whole endostyle or  $\frac{1}{2}$  the epithelial investment of the simple endostyle of *Tunicates* or *Amphioxus*.

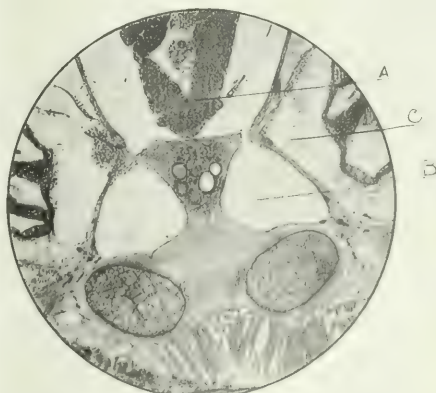


FIG. 7.—Photomicrograph of cross-section of thyroid area in a recently metamorphosed *Ammocetes branchialis* showing relation of follicles to (A) tongue, (B) blood spaces, (C) gills.





means of its mucinous secretions it certainly subserves a function of prime importance in the nutrition of these animals.

#### SUMMARY.

Tunicates, Amphioxus and Ammocoetes are the only classes of animals which possess well developed endostyles. Goodsir, Müller, Schneider, Dohrn and all subsequent observers have shown that morphologically the endostyles are fundamentally identical in all. Cyclostomes, fishes, amphibians, reptiles, birds and mammals are the only classes of animals which possess ductless thyroids, the follicles of which are anatomically identical in all. The demonstration of the ontogenetic relationship between the endostylar mechanism and the true thyroid has been made possible through the preservation of a single class of chordates—the Cyclostomes—and the discovery by Schneider that during the metamorphosis of Ammocoetes into Petromyzon, typical ductless thyroid follicles are formed from the endostyle and as I have shown (*Jour. Exp. Med.*, 1913, XVII, No. 4) out of one and possibly two persistent epithelia. The most important of the epithelia concerned in the formation of the ductless follicles is that form which is continuous with the lining epithelium of the duct and pharyngeal grooves. Additional data of this relationship are afforded by the observations of Dohrn that in some of the lower fishes a transient system of peripharyngeal grooves is present in the earlier stages of embryological development. This overlapping, so to speak, of the endostylar mechanism of the lowest chordates onto the ductless thyroid mechanism of the higher chordates is as firmly established as morphological studies make possible. Studies in the embryology of the duct-

less thyroid have shown that in fishes, amphibians, reptiles and birds the thyroid arises solely from a median, single, ventral downgrowth of the pharyngeal entoderm in or slightly anterior to the first aortic arch. In mammals this symmetry of development was believed to be departed from through the discovery by Stieda of the so-called "lateral thyroid anlagen" from the fourth or more accurately in man the rudimentary fifth gill pouch, but the work in the embryology, in the pathology and in the developmental defects of the thyroid during recent years has shown that these lateral bodies which in mammals only become imbedded in the lateral thyroid lobes take no part in the formation of thyroid gland tissue. This solution of the origin of the mammalian thyroid from the single median anlage harmonizes the location and development of the endostyle with the location and development of the ductless thyroid. The thyroid mechanism, therefore, irrespective of the possible phylogenetic relationship to the chordate stem of the several classes of animals concerned, appears to have been evolved through a direct line of descent from the Tunicates through the Amphioxus, fishes, amphibians, reptiles, birds and mammals. The meager evidence of the physiology in both the endostyle and the ductless thyroid gives no suggestion of an inter-relationship or function. Primarily the thyroid is a part of the alimentary tract and in its endostylar form is a digestive gland of great importance through its probable external secretion. In its ductless form it is only the atrophic remnant of its ancestor which, while it has suffered a corresponding distortion of function, still profoundly influences the animal's nutrition through the effect of its probable internal secretion.

## HYPERSENSITIVENESS TO TUBERCULO-PROTEIN AND TO TUBERCULIN.\*

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Few problems in experimental medicine have stimulated so much work, or have given rise to so large a literature, in a short period of time, as has the subject of anaphylaxis. In the course of a brief decade numerous articles dealing with it have appeared, and, although in a measure polemic in nature, a substantial harvest of facts may be gathered when the chaff is cleared away.

A great deal has been published concerning hypersensitiveness to bacterial proteins, and from the data in the literature several facts seem established: Animals can be actively sensitized with dead bacteria, or with the extracts of them. The hypersensitive state is transmitted from mother to young. A refractory state is readily induced, and, in general, sensitization due to bacterial proteins obeys the same laws as does sensitization due to any other protein. Further, the symp-

toms resulting when a sensitized guinea pig is given an intoxicating dose of the homologous bacterial protein are in kind the same as those seen in hypersensitiveness to serum.

However, striking as is the similarity of the phenomena developing after sensitization with serum, and with proteins of bacterial origin, one apparent difference is to be noted. The injection of horse serum into a series of guinea pigs leads to the development of a state in which the animal is so sensitive that a second dose, properly administered, causes, in the majority of instances, acute lethal shock, whereas experiments published concerning hypersensitiveness to bacterial proteins give the impression that sensitization here is much less constant and much less intense. Citation of a few of the more important articles on this phase of the subject will serve to illustrate these points.

Rosenau and Anderson<sup>1</sup> conducted experiments on guinea pigs with extracts of cholera, typhoid, hay, anthrax, tubercle

\* Read at a meeting of The Laennec, a Society for the study of Tuberculosis, The Johns Hopkins Hospital, January 27, 1913.

and subtilis bacilli. After an incubation period of 11 days or more, these animals reacted to a second dose of the specific protein, which caused no symptoms in the controls. It is noteworthy, however, that the reactions produced were never so intense as in the experiments with serum or with milk, and in no instance led to acute death.

Axamit<sup>3</sup> succeeded in sensitizing guinea pigs and rabbits with aqueous extracts of a variety of yeast obtained from a skin lesion. Here, again, the production of acute fatal shock was not noted.

Kraus and Steinitzer<sup>4</sup> produced in horses and goats "mild, or moderately severe" sensitization with typhoid bacilli.

Kraus and Doerr<sup>5</sup> sensitized guinea pigs with small amounts of typhoid and of dysentery bacilli, with the vibrio of cholera and with other vibrios and observed that, in only a small percentage of animals did acute lethal shock follow a second injection.

Tscharnotzkis,<sup>6</sup> in a large series of experiments with bacterial extracts made by heating the organisms in normal saline solution at 56° to 60° C. for an hour, concluded that the protein of typhoid, dysentery, cholera, pseudo cholera or of prodigious cultures can render animals hypersensitive; that for hypersensitiveness to develop a longer incubation period is necessary than in sensitization with serum, or with milk; and, finally, that though the state produced is a specific one, the symptoms elicited are never so intense as are those seen in hypersensitiveness to serum.

E. C. Rosenow<sup>7</sup> injected guinea pigs with dead pneumococci and with pneumococcus extracts. He clearly established the fact that animals can be sensitized by treatment with these substances and that the constancy with which hypersensitiveness develops depends upon the use of sufficient protein. He showed further that the hypersensitive condition is transmitted from the mother to her offspring, and that passive sensitization resulted when a normal animal was injected with the serum of an actively sensitized one.

P. Th. Müller<sup>8</sup> demonstrated that the constancy with which sensitization could be produced by injecting guinea pigs with *B. typhosus*, *coli*, *dysenteriae*, *diphtheriae* and with streptococci varied directly with the amount of specific protein employed.

Friedberger and Mita<sup>9</sup> showed that no real difference exists in the regularity with which acute death can be produced in animals sensitized with bacteria and with serum, provided the amounts of bacterial protein used for preparation and for reinjection approximate those used in producing hypersensitiveness to serum.

They interpret the failure of many observers to produce sensitization with tuberculin as due to the minimal tuberculo-protein content of that preparation, and regard the tuberculin reaction as a true anaphylactic phenomenon.

Baldwin,<sup>10</sup> in 1910, described in detail the manifestations produced in guinea pigs by treatment with aqueous extracts of tubercle bacilli. He demonstrated that a true sensitization could be produced with the watery extracts of this organism, the most striking results being obtained when the preliminary injection was given into the peritoneum and when the intoxi-

cating dose was injected by the post-orbital route. He stated that as little as 0.0008 gm. of the dry protein is sufficient to sensitize a normal guinea pig; that probably even less is required, and that 0.0004 gm. suffices to produce fatal sensitization in 22 days. He also described in detail other characteristics of the state produced by the injection of tuberculo-protein and pointed out the similarity of active sensitization with it and with serum, the maternal transmission of the condition to the offspring and the possibility of causing a refractory or anti-anaphylactic state with it.

This paper is replete with valuable data and pregnant with ideas.

A. K. Krause,<sup>11</sup> in the following year, continued studies along the same line, investigating, among other things, the routes best suited for sensitization and for intoxication, the optimum incubation period for the development of maximum hypersensitiveness, the preparations best adapted to the work and the quantitative interrelation of these factors. He noted that practically any parenteral route by which a sufficient quantity of tuberculo-protein can be introduced may be used in sensitizing an animal; that acute anaphylaxis may be produced by toxic injections given into the post-orbital space or into a vein, and that there is no choice of method, except that of ease and availability. Krause found that sensitization can be obtained with 0.00005 gm. of tuberculo-protein, that the shortest incubation period was six days and the longest duration of the hypersensitive state was 286 days, although he believed it probable that sensitization lasts throughout life as does hypersensitiveness to serum.

Krause was unable to produce passive hypersensitiveness with the serum of sensitized animals, but stated that "further work no doubt will show that this apparent difference between the action of tuberculo-protein and serum protein is a quantitative, rather than a qualitative difference."

To all workers in the field of anaphylaxis it is a well known fact that in order to produce acute shock, amounts of protein smaller than certain established minima cannot be used. It is clear, from the published work of numerous observers, that when minimal quantities of protein, or amounts approaching this minimum are employed, the results obtained are inconstant, and that constant findings may be anticipated only when larger quantities of the material are injected.

The amounts of various sera required constantly to produce maximal hypersensitiveness have been accurately determined, but the studies of sensitization with bacterial proteins undertaken from a quantitative standpoint are few. Most of the workers in the field of bacterial anaphylaxis have designated the dosage employed by them in terms of "ösen" s, or of "cultures," apparently failing to recognize how variable the amount of organisms in a culture of different bacteria may be. Enormous amounts of bacteria, styled large sensitizing or large intoxicating doses, often signify, in reality, small amounts of protein material, inasmuch as only about 50 per cent of the dry organism, or approximately 15 per cent of the wet, is protein in nature. This fact makes it clear why many of those who have attempted to produce sensitization with



bacteria have failed, for they were working with infinitesimal quantities of essential material. Positive results can be hoped for only when better technic is employed, when quantities sufficiently large are used in the experiment.

With these facts in mind, and in an endeavor to determine if acute lethal shock can be induced constantly after sensitization with the protein of tubercle bacilli, the following experiments were undertaken.

#### PREPARATION OF THE TUBERCULO-PROTEIN.

Several strains of tubercle bacilli of human type were used. Two of them, H $\alpha$  and H $\beta$  were isolated from the sputum of two patients of the Phipps Tuberculosis Dispensary of the Johns Hopkins Hospital, and one, H 39, was received from the Saranac Laboratory, through the courtesy of Dr. A. K. Krause. These strains were inoculated into many flasks of 5 per cent glycerin broth, and the growth washed with sterile distilled water until broth free. The mass of bacilli was then heated for two hours at 55° to 60° C., desiccated in vacuo and thoroughly ground to a powder. Each gram of the pulverized bacilli was then extracted with 15 ccm. of sterile distilled water, at 55° C. for from 48 to 72 hours and then filtered through a Berkefeld bougie. A clear, amber-yellow fluid was the end-product and with the addition of a little toluol as preservative, was used as the antigen. The quantitative estimations of the alcohol precipitable protein in this solution showed a content varying from 0.005 to 0.009 gm., in a cubic centimeter. In all the experiments the guinea pig was the animal of choice and, in as far as possible, animals of the same weight were used in parallel experiments.

#### METHOD OF INJECTION.

(a) A short series of preliminary experiments gave complete confirmation of Baldwin's observation that injection into the peritoneal cavity offers a ready route by which the protein may be introduced, leading to active sensitization of the animal, with minimal effort on the part of the experimenter, and with very little risk to the animal.

(b) For intoxication several methods were employed in the attempt specifically to shock the sensitized animals. In the protocols which follow, it will be seen that injections were made into the sub-dural space by the post-orbital route; into the right ventricle of the heart, or into the jugular vein.

For the post-orbital injections, the technic of Gay and Southard was used. A fine needle was introduced through the cocaineized conjunctiva, near the median canthus of the eye, so as to skirt the eye-ball and enter the optic foramen. The warm fluid was then slowly injected into the subdural space beneath the pons. The method is easy of application, but occasionally, in spite of apparently correct technic, the solution returns through the nose.

Following the injection, even when slowly made, there is, not infrequently, transitory coma lasting 2 to 5 seconds, vertigo, sneezing and restlessness. In occasional instances, death may occur from pontile hemorrhage. Using this

method, as much as 1.1 ccm. may be safely inoculated into a full grown guinea pig.

For the intracardiac injections, the technic of P. A. Lewis was followed. The chest of the animal shaved, a small needle

TABLE I.  
Determination of the Primary Toxicity of Tuberculo-Protein.

Number of Guinea Pig	Weight	Mode of Injection	Amount of Hypertel	Remarks
	Grams		Grams	
44	310	Intraperitoneal	0.002	No symptoms.
45	290	" "	0.002	Do.
46	275	" "	0.005	Do.
47	260	" "	0.005	Transitory restlessness and bucking.
48	275	" "	0.010	No symptoms.
49	270	" "	0.020	Do.
50	300	" "	0.050	Do.
192	290	" "	0.100	Do.
194	320	" "	0.200	Transitory restlessness and sneezing.
197	280	" "	0.200	Do.
52	250	Post-orbital	0.002	No symptoms.
56	265	" "	0.002	No symptoms. Part returned through nose.
57	275	" "	0.005	Restless, sneezing. Part returned through nose.
58	240	" "	0.005	No symptoms.
59	260	" "	0.010	Vertigo, sneezing, restless. Recovery.
62	280	" "	0.010	Transitory restlessness and sneezing.
63	230	" "	0.010	Transitory restlessness. Frequent urination.
64	220	" "	0.010	Frequent urination and defecation.
66	250	" "	0.010	Coma 20 secs. Recovery in 3 min.
67	255	" "	0.015	Part returned through nose. Sneezing, restless.
68	270	" "	0.015	No symptoms.
69	268	" "	0.015	Death immediate. Pontile hemorrhage.
76	240	Intracardiac	0.005	No symptoms.
77	260	" "	0.005	Restless. Frequent defecation.
79	250	" "	0.010	No symptoms.
82	270	" "	0.010	Death in 20 mins. Pericardial hemorrhage.
84	292	" "	0.015	Death in 50 mins. Pericardial hemorrhage.
85	280	" "	0.015	No symptoms.
86	270	" "	0.022	Dyspnea, dull. Death in 5 hrs. Hemorrhage.
87	280	" "	0.022	No symptoms.
91	300	Intravenous	0.005	Do.
92	285	" "	0.010	Transitory dyspnea. Defecation.
98	310	" "	0.010	No symptoms.
99	275	" "	0.015	Restlessness.
100	290	" "	0.022	No symptoms.
101	315	" "	0.025	Do.
102	290	" "	0.030	Death in 20 secs. Dilated right heart.
103	280	" "	0.030	Transitory coma. Recovery in 10 mins.

was thrust through the fourth or fifth left interspace and when a spurt of blood returned into the syringe, the fluid was slowly injected. By this procedure, we have been able to introduce as much as 2.5 ccm. of fluid without serious consequences to the animal. Transitory restlessness, bucking move-

ments and tachypnea are frequently noted, and many animals succumb from hemorrhage into the pericardial or pleural sacs.

For intravenous injection, the method of Friedberger was employed. A guinea pig was lightly etherized, and fastened by means of tape upon its back, the upper jaw as well as the legs being firmly fixed. The right jugular vein was dissected free and two ligatures loosely laid about it. Several hours later, after the animal had recovered its normal temperature, it was again fixed on the table and the injection made into the isolated vein. Complicated though this procedure may seem, it is readily and quickly executed and is rarely attended by any serious results to the animal. We have introduced as much as 3.5 ccm. of fluid by this method, without causing evident symptoms other than slight transitory restlessness and tachypnea.

#### DETERMINATION OF THE PRIMARY TOXICITY OF THE ANTIGEN.

Injections of varying amounts of the tuberculo-protein were made by the intraperitoneal, intracardiac, intravenous and post-orbital routes, to determine the minimal lethal dose of the preparation. A study of Table I will show that the extract was practically non-toxic, for of all the 38 untreated animals injected with amounts of from 0.002 to 0.200 gm., none succumbed from the primary toxic action of the test preparation. The non-toxicity of these aqueous extracts of tubercle bacilli confirms the observation of Vaughan," made in 1907.

TABLE II.  
Determination of the Sensitizing Dose of Tuberculo-Protein.

Number of Guinea Pig	Weight	Preliminary Treatment	Interval	Secondary Treatment	Remarks
	Grams	Grams Protein	Days	Grams Protein	
		Intra-peritoneal Injection		Post-Orbital Injection	
110	300	0.0005	15	0.0025	No symptoms.
111	280	0.0005	15	0.0025	Death in 1 min. Pontile hemorrhage.
112	295	0.0005	15	0.005	No symptoms.
113	290	0.0005	19	0.005	Sneezing, convulsions. Death in 30 secs. Typical post mortem findings.
114	300	0.0005	19	0.008	No symptoms.
115	300	0.0005	19	0.008	Pressure symptoms, vertigo, unrest. Recovery in 30 mins.
		Intra-venous Injection			
123	300	0.0005	14	0.005	No symptoms.
124	350	0.0005	14	0.005	Death from hemorrhage into pericardium.
125	380	0.0005	14	0.005	No symptoms.
126	400	0.0005	14	0.008	Do.
127	360	0.0005	18	0.008	Dyspnea, clonic convulsions. Death in 4 mins. Typical findings.
128	320	0.0005	18	0.010	Death from hemorrhage into pericardium.
		Intra-venous Injection			
129	300	0.0005	21	0.005	No symptoms.
130	320	0.0005	21	0.005	Do.
131	300	0.0005	21	0.008	Do.
132	310	0.0005	21	0.008	Do.

TABLE II.—Continued.

Number of Guinea Pig	Weight	Preliminary Treatment	Interval	Secondary Treatment	Remarks
	Grams	Grams Protein	Days	Grams Protein	
				Post-Orbital Injection	
133	270	0.0010	18	0.005	Do.
134	285	0.0010	18	0.005	Clonic convulsions, sneezing. Death in 18 mins. Typical findings.
135	260	0.0010	19	0.005	Clonic convulsions.
136	255	0.0015	19	0.005	Do.
137	260	0.0015	19	0.005	Death from pontile hemorrhage
138	270	0.0025	19	0.005	Sneezing, bucking, unrest. Recovery prompt.
139	285	0.0025	19	0.005	No symptoms.
140	280	0.0025	19	0.005	Vertigo, unrest, urination, defecation. Recovery prompt.
141	270	0.0035	17	0.005	Sneezing, dyspnea, pollakiuria. Recovery.
142	275	0.0035	17	0.005	Dyspnea, paresis of hind legs. Recovery.
143	260	0.0035	17	0.005	No symptoms.
144	270	0.0035	17	0.005	Do.
151	270	0.0045	17	0.005	Dyspnea, paresis of hind legs. Death in 18 mins. Typical findings.
153	290	0.0045	17	0.005	Dyspnea, bucking, clonic convulsions. Death in 7 mins. Typical findings.
154	275	0.0045	17	0.005	No symptoms.
156	255	0.0045	17	0.005	Part of fluid through nose. Restless, sneezing. Recovery.
157	283	0.0045	17	0.005	No symptoms.
158	280	0.005	17	0.005	Dyspnea, clonic convulsions. Death in 3 mins. Typical findings.
160	270	0.005	17	0.005	Clonic convulsions, gasping and bucking. Death in 5 mins. Typical findings.
161	280	0.005	17	0.005	Death from pressure?
162	290	0.005	20	0.005	Dyspnea, paresis of hind legs, hyperesthesia, fall in temp. Recovery.
163	298	0.005	20	0.005	Part of fluid lost through nose. Sneezing, unrest. Recovery.
165	270	0.008	15	0.005	No symptoms.
166	300	0.008	15	0.005	Dyspnea, clonic spasms, cyanosis. Death in 4 mins. Typical findings.
168	290	0.008	17	0.005	Coma, gasping, clonic spasms. Death in 2 mins. Typical findings.
169	260	0.008	17	0.005	Bucking, sneezing, convulsions, paresis of legs. Death. Typical findings.
170	300	0.008	17	0.005	Death from faulty technic of injection.

#### DETERMINATION OF THE OPTIMUM SENSITIZING DOSE.

The attempt was made to establish the amount of tuberculo-protein which, when introduced into the peritoneal cavity of a guinea pig, would constantly sensitize it, so that a small amount of the antigen, injected by the intracardiac, intravenous or post-orbital route, would constantly elicit signs of acute hypersensitiveness. To this end, a series of normal guinea pigs were given intraperitoneal injections of tuberculo-protein varying in amount from 0.0025 to 0.025 gm., and after a period of from 10 to 24 days, these animals were reinjected with different amounts of the antigen, from 0.0025 to 0.01 gm., and the results noted. For controls, untreated

guinea pigs were given the same amount of protein by the same route as was used to shock the sensitized animals. The tables show the results of these experiments.

TABLE III.  
Preliminary Treatment with Double the Sensitizing Dose.

Number of Guinea Pig	Weight	Preliminary Treatment	Interval	Secondary Treatment	REMARKS
	Grams	Guinea Protein	Days	Guinea Protein	
		Intra-peritoneal Injection		Post-Orbital Injection	
176	290	0.016	19	0.008	Dyspnea, clonic convulsions, coma. Death in 11 mins. Typical findings.
177	275	0.016	19	0.008	Bucking, sneezing, gasping. Death in 6 mins. Typical findings.
178	320	0.016	19	0.008	Death from pressure. Lungs collapsed and congested.
179	310	0.016	19	0.008	Clonic convulsions, coma, dyspnea. Death in 9 mins. Typical findings.
180	320	0.016	19	0.008	Transitory dyspnea, sneezing and unrest. Recovery in 4 hours.
181	320	0.016	19	0.008	Dyspnea, paresis of hind legs, coma. Death in 5 mins. Typical findings.
182	300	0.016	19	0.008	Faulty technic. Fluid returned through nose.
183	320	0.016	19	0.008	Dyspnea, clonic convulsions. Death in 8 mins. Typical findings.
				Intra-cardiac Injection	
185	295	0.016	19	0.008	Coma with convulsions and gasping respiration. Death in 5 mins. Typical findings.
186	280	0.016	19	0.008	Death from pericardial hemorrhage.
187	310	0.016	19	0.008	Clonic convulsions, dyspnea, coma. Death in 4 mins. Typical findings.
188	290	0.016	19	0.008	Clonic convulsions, paresis hind legs, dyspnea. Death in 12 mins. Typical findings.
189	300	0.016	19	0.008	Coma, dyspnea. Death in 50 secs. Typical findings.
190	280	0.016	19	0.008	Death from pericardial hemorrhage.
				Intra-venous Injection	
171	320	0.010	19	0.008	Dyspnea, cyanosis, convulsions. Death in 6 mins. Typical findings.
172	340	0.010	19	0.008	Dyspnea, convulsions, coma. Death in 7 mins. Typical findings.
173	400	0.016	19	0.008	Gasping respiration, convulsions, paresis of hind legs. Death 11 mins. Typical findings.
174	295	0.016	19	0.008	Bucking, sneezing, convulsions. Death in 6 mins. Typical findings.
175	280	0.016	19	0.008	Clonic convulsions, gasping respiration. Death in 3 mins. Typical findings.
176	290	0.016	19	0.008	Transitory dyspnea and restlessness. Recovery.

(Four animals in this series died due to errors in technic—of the remaining 16, 14 showed lethal hypersensitiveness = 87.5%.)

Twenty guinea pigs, sensitized by the intraperitoneal injection of 0.008 gm. of tuberculo-protein, were tested 16 days later by an intravenous or an intracardiac injection of

0.005 gm. of the protein. The results are analogous to those tabulated.

Analysis of these results shows that although, in an isolated instance, it is possible to sensitize with quantities of the protein as small as 0.0005 gm., that sensitization with this dose is most irregular. It is further evident that the results are more constant and the symptoms more severe when doses larger than 0.003 gm. are used, and that in order regularly to produce maximum hypersensitiveness, an injection of at least 0.008 gm. of our preparation is necessary. It was found, too, that the optimum incubation period is between 14 and 23 days.

Using twice the amount of protein required regularly to sensitize guinea pigs, acute shock was produced by the re-injection of 0.008 gm. of protein in 87.5 per cent of the animals.

The amount of protein used for sensitization caused no variation in the incubation period required, nor did the use of repeated small doses cause any change in the end result, except that by this means more protein could be safely injected. Animals receiving protein daily, or at short intervals, and tested in less than the incubation period noted, are refractory to intoxicating injections.

The quantity of tuberculo-protein required regularly to elicit the signs of anaphylaxis in a properly prepared animal varies from 0.0025 to 0.008 gm., with 0.005 gm. as an efficient intoxicating dose in well prepared animals.

In six guinea pigs sensitization persisted for 490 days, and we agree with Krause that in all probability further work will show that this state of hypersensitiveness persists throughout the life of the animal.

#### MATERNAL TRANSMISSION OF THE HYPERSENSITIVE STATE TO THE OFFSPRING AND THE DURATION OF THIS INHERITED HYPERSENSITIVENESS.

Six female guinea pigs, actively sensitized 18 days before by the intraperitoneal injection of 0.008 gm. of tuberculo-protein, were caged with two normal untreated bucks. Four of these females became pregnant and each gave birth to three young. Paralleling the work of Rosenau and Anderson on the maternal transmission of hypersensitiveness to horse serum, we sought to exclude milk as the transmitting factor. Six of these young guinea pigs were therefore placed to nurse an untreated female and the offspring of this normal mother placed to nurse the hypersensitive female. After four, six and nine weeks, respectively, the young of the sensitized and of the non-sensitized females were tested, with the following results:

Two guinea pigs born of sensitized mother No. 188, and nursed by her, succumbed with acute shock; one failed to react. Three of the six young, born of sensitized females Nos. 189 and 196, and nursed by untreated guinea pigs, died in acute shock, whereas three showed only slight symptoms and recovered. None of the five guinea pigs born of normal mothers showed any symptoms when injected with tuberculo-protein.



This short series of exchange experiments shows that hypersensitiveness to tuberculo-protein is transmitted from the mother, and that the milk plays no rôle in this transmission.

Twelve guinea pigs born of five untreated females, impregnated by sensitized males, were not hypersensitive to tuberculo-protein. Females sensitized before the beginning of pregnancy, early, or late in the course of it, in the few instances studied, transmitted the hypersensitive state to the offspring. The regularity with which hypersensitiveness is transmitted to the young varies, to some extent, with the degree of hypersensitiveness of the mother.

Two animals with inherited hypersensitiveness, tested 120 and 175 days after birth, respectively, showed signs of acute hypersensitiveness.

#### PASSIVE SENSITIZATION TO TUBERCULO-PROTEIN.

Twenty-two attempts were made to transfer hypersensitiveness to tuberculo-protein from actively sensitized guinea pigs to untreated animals of the same species. Quantities of fresh serum or of citrated whole blood obtained from 16 hypersensitive animals, varying from 1 to 6.5 ccm. in amount, were injected into the peritoneal cavity of normal guinea pigs. Of the 22 animals so treated, three died before they were tested. The remaining 19 were given post-orbital injections of 0.008 gm. of the tuberculo-protein, 22 to 42 hours after the preparing dose. Four of these animals succumbed in 3 to 18 minutes, with the symptoms of acute hypersensitiveness, and post mortem showed the typical massive pulmonary emphysema, sub-epicardial hemorrhages and delayed coagulation time; three died as the result of faulty technic; and in the remaining 12, no symptoms developed. The controls were all negative.

In this series of experiments, it was striking that passive sensitization was inconstant in its development, but that it could be brought about with greater regularity when the donor of the serum or blood had been treated with at least 0.008 gm. of the protein.

Passive heterologous hypersensitiveness from rabbits to guinea pigs was successfully produced in three of 14 attempts. In each instance the rabbit received, intraperitoneally, 0.005 gm. of protein per 100 gm. of body weight, and 18 days later 4 ccm. of the rabbit serum, in divided doses, were injected into the peritoneal cavities of untreated guinea pigs. The guinea pigs were then tested after an incubation period of 40 hours by an injection of 0.008 gm. of tuberculo-protein injected into the post-orbital space.

To recapitulate:

These experiments confirm the already demonstrated facts that:

1. A protein substance can be obtained by the extraction of tubercle bacilli with water, and with it animals can be actively sensitized.
2. A refractory condition to this protein can be produced.
3. The hypersensitive condition is transmitted from mother to young.

These experiments establish further that:

1. Active sensitization induced by treatment with this protein may be as regular in its development and as intense in its manifestations as is that produced by treatment with other proteins.

2. Passive homologous and heterologous hypersensitiveness can occasionally be produced with the blood or with the serum of an actively sensitized animal.

3. The material transmission of the hypersensitiveness does not take place through the milk.

4. The regularity with which maximum hypersensitiveness can be produced is largely dependent on the use of a sufficient amount of protein in preparing and in testing the animals.

To warrant the application of the demonstrated facts to assist in interpreting the phenomena that develop when tuberculin is administered to a host infected with the tubercle bacillus, the identification of the protein used in these experiments with the essential protein of tuberculin seemed desirable.

Some evidence that such an identity could be established had already been furnished by Baldwin and by Krause, who produced lethal anaphylactic shock by injecting tuberculous guinea pigs with old tuberculin.

In the following experiments it will be shown that tuberculous guinea pigs do develop symptoms of hypersensitiveness following the injection of "tuberculo-protein," of "old tuberculin," or of albumose-free tuberculin into the heart or into the subdural space; and further, that cross sensitization with these preparations is readily produced.

#### THE INTOXICATION OF TUBERCULOUS GUINEA PIGS.

The guinea pigs used in these experiments had each received an injection of 0.001 gm. of a culture of H 39 beneath the skin of the right groin 61 days before the tests were made. To bring about the intoxication of these animals, post-orbital or intracardiac injections of the several proteins were made.

Of 12 tuberculous animals tested, one of the four injected with old tuberculin showed signs of hypersensitiveness, two of the four tested with albumose-free tuberculin succumbed with signs of acute shock, and one of the four tested with "tuberculo-protein" developed lethal hypersensitiveness.

#### CROSS SENSITIZATION EXPERIMENTS.

##### PREPARATION OF THE PROTEINS TESTED.

The proteins used in these experiments were as follows:

A. Tuberculo-protein, the protein obtained by the aqueous extraction of ground tubercle bacilli in the manner already detailed.

B. "O. T. Protein," the protein obtained from old tuberculin. The tuberculin itself was used in only a few experiments, inasmuch as the large content of glycerin and of salts make it an undesirable antigen. To remove these constituents, the tuberculin was treated as follows: 4 ccm. of old tuberculin, diluted with distilled water to about 12 ccm., were treated with an equal amount of 10 per cent sodium hydrate for 36

hours at 55° C., then filtered and precipitated with ten volumes of absolute alcohol. The white flocculi formed were dried in vacuo, redissolved in distilled water, neutralized with  $\frac{1}{N}$  hydrochloric acid and again precipitated with absolute alcohol. The precipitate, after desiccation in vacuo, was then ground and the white powder thus obtained used as antigen. Although undoubtedly rich in peptone, this material is less irritating to the guinea pig and is appreciably less toxic than commercial old tuberculin.

C. "A. F. Protein"—Albumose-Free Tuberculin. Inasmuch as this tuberculin contains no nitrogenous material except that from the tubercle bacillus and asparagin, it has a very low primary toxicity. In the experiments to follow, the untreated commercial preparation was therefore employed.

#### METHOD OF IDENTIFYING THE PROTEINS.

No attempt was made chemically to identify the preparations used. The facts obtained were derived from experiments made to determine if sensitization of an animal with one protein caused hypersensitiveness to the others. The method was as follows:

A number of guinea pigs were each given eight daily intraperitoneal injections of 60 mgm. of the powdered "O. T. Protein," and after an incubation period of 17 days were tested by an intracardiac injection of 0.015 mgm. of "tuberculo-protein," or of 2 ccm. of "A. F. Protein." Similarly, guinea pigs sensitized by two intraperitoneal injections each of 1 ccm. of A. F. Tuberculin after 17 days were given a post-orbital or an intracardiac injection of 0.015 mgm. of "tuberculo-protein," or 1 ccm. of "A. F. Protein"; and guinea pigs sensitized by an intraperitoneal injection of 0.015 mgm. of "tuberculo-protein" were similarly tested with "A. F. Protein."

In none of the experiments was the "O. T. Protein" used to intoxicate sensitized animals because of its primary toxicity, due probably to its peptone content.

These experiments clearly demonstrated that preliminary treatment of guinea pigs with "O. T. Protein," "A. F. Protein," or with "Tuberculo-Protein," causes the development of hypersensitiveness to "A. F. Protein" and to "Tuberculo-Protein."

This is sufficient evidence to prove the general assumption concerning the identity of the essential protein of tuberculin used to demonstrate the reaction in man, with the tuberculo-protein shown to produce classical hypersensitiveness in animals. The demonstration of this fact justifies the application of the data obtained in the experiments on animals with

tuberculo-protein to the interpretation of the phenomenon known as the tuberculin reaction.

Wolff-Eisner,<sup>12</sup> v. Pirquet,<sup>13</sup> Baldwin,<sup>14</sup> Krause,<sup>15</sup> Hamman and Wolman,<sup>16</sup> and many others regard this phenomenon as a manifestation of hypersensitiveness to tuberculin. For this view the presumptive evidence is strong. The facts which support this hypothesis may be briefly summarized as follows:

All the manifestations of typical hypersensitiveness to protein can be produced in guinea pigs by treatment with aqueous extracts of tubercle bacilli. Guinea pigs can be sensitized with albumose-free tuberculin and with old tuberculin that has been freed of glycerin and made poor in salts. And sensitization with any of these products causes the animal to react to injections of the others.

Hypersensitiveness to tuberculin develops within 7 to 15 days after infection with the *B. tuberculosis*.

Tuberculous animals can occasionally be intoxicated with tuberculo-protein, developing symptoms of hypersensitiveness.

The passive transference of hypersensitiveness from a tuberculous man to normal guinea pigs has been successfully accomplished<sup>17</sup> and positive results have likewise been obtained when the serum of a sensitized animal has been injected into an untreated one.

The type of the reaction symptoms and the development of them in an infected host after the administration of minimum doses of tuberculin are likewise suggestive facts.

This evidence justifies the interpretation of the tuberculin reaction as a manifestation of true hypersensitiveness.

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## THE ANCIENT OFFICE OF CORONER.\*

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*If there be found a slain person in the land which the Lord thy God giveth thee to possess it, lying in the field, and it be not known who hath slain him; then shall thy elders and thy judges go forth, and they shall measure unto the cities which are round about the one that is slain. And it shall be that the city which is nearest unto the slain person, even the elders of that city shall take a heifer, which hath not been wrought with, which hath not drawn in a yoke; and the elders of that city shall bring down the heifer unto a rough valley, which is neither tilled nor sown, and they shall break the neck of the heifer in the valley; And the priests, the sons of Levi, shall come near; for them the Lord thy God hath chosen to minister unto Him, and to bless the name of the Lord; and after their decision shall be done at every controversy and every injury; And all the elders of that city who are nearest unto the slain person shall wash their hands over the heifer, the neck of which is broken in the valley. And they shall commence and say, Our hands have not shed this blood, and our eyes have not seen it. Grant pardon unto Thy people Israel, whom Thou hast redeemed, O Lord, and lay not innocent blood in the midst of Thy people Israel; and the blood shall be forgiven unto them. And thou shalt put away the guilt of the innocent blood from the midst of thee, when thou wilt do what is right in the eyes of the Lord. Deut. XXI, 1-9.*

This passage from the Bible will illustrate the fact that a legal inquiry into all cases of violent death or deaths due to unknown causes has been practiced by enlightened nations from time immemorial. So, indeed, we find that in all civilized countries of our day, there is some form of preliminary investigation or other, wherever there is reason to believe that a deceased person came to his death through violent or unfair means, or by culpable or negligent conduct of himself or others, and not through pure accident or mischance. The necessity for such an investigation is self-evident and is recognized by all, and it is usual to conduct it without delay and by competent officers, and, if necessary, without anybody being accused: in fact it is to afford evidence of the necessity or otherwise of anybody being accused that the investigation is of greatest use. The mode of conducting such an investigation, however, varies in different countries. In France it is conducted by an officer somewhat similar to our district attorney and called the *procureur de la république*, who is assisted by a proper medical expert; in Germany, there is a similar judicial officer named the *Staatsanwalt*; in Russia, Denmark, and other European countries the procedure is essentially the same as in France or Germany, that is the case is investigated by the ordinary state's attorneys, who call for assistance upon expert medical men. It is to the English law that the honor belongs of designating an especial officer for this important function, the coroner, who represents the king as a caretaker of the lives of the people, and provides that every violent death or sudden death with cause unknown shall be subject to public inquest by a jury of\*not less than twelve good and

lawful citizens. This is still the practice among most of the English-speaking nations, that is in England and her Colonies, with the exception of Scotland, and in most of the United States.

The coroner is so-called *à coronâ*, because he is an officer of the crown, and this name, or variations of it, have been used for many years. He was called *coronarius*<sup>1</sup> in the reign of Henry II. He was styled *custos placitorum coronæ*<sup>2</sup> in the reign of Richard I, and in the Magna Charta and subsequent statutes he is known as *coronator*.

The office of coroner is of so great antiquity that its commencement is not definitely known.<sup>3</sup> Its origin is usually ascribed to the Articles of the Eyre of 1194, but it is probably much earlier. By some it is said to be coeval with that other distinctly English office, that of the sheriff, and to have been ordained with the latter office to keep the peace when the earls gave up the wardship of the county. At any rate we know that coroners existed in the time of King Alfred,<sup>4</sup> and this office is also mentioned in the charter granted by King Athelstan to the monastery of St. John of Beverley in 925.<sup>5</sup> We thus see that this office is nearly a thousand years old.

The duties of the coroner in his earlier days embraced a much wider sphere of activity than at the present time.<sup>6</sup> Thus from 4 Edward I. St. 2 (*Officium Coronatoris*) it appears that:

a coroner of our lord the king ought to inquire of these things: First, when coroners are commanded by the king's bailiffs or by the honest men of the county, they shall go to the places where any be slain, or suddenly dead or wounded, or where houses are broken, or where treasure is said to be found, and shall forthwith command four of the next towns, or five, or six, to appear before him in such a place; and when they are come thither, the coroner upon the oath of them shall inquire in this manner, that is, to ask, if it concerns a man slain, if they know when the person was slain, whether it were in any house, field, bed, tavern, or company, and if any, and who were there, etc. It shall also be inquired if the dead person were known, or be a stranger, and where he lay the night before. And if any person is said to be guilty of the murder, the coroner shall go to their house and inquire, etc.

Thus we note that his duties were not confined to cases of sudden or violent death. Indeed on examining the old documents we find that they extended over a wide range of criminal matters and even to civil pleas (Gross'). In the thirteenth century coroners were the principal agents in bringing all sorts of criminals to justice. They held inquests not only in cases of sudden, violent, or unnatural deaths, but also in cases of serious bodily injury, burglary, arson, rape, prison-breaking, and concealment of treasure-trove or wreck. They received the declarations of approvers, and heard criminal accusations of one person against another, the final trial being reserved for the eyre. They kept, moreover, a record of outlawries, and received the confession and abjuration oath of felons who had fled to sanctuary. They furthermore some-

\* Paper read at a meeting of The Johns Hopkins Medical Society, January 6, 1913.



times exercised judicial powers, by virtue of their appointment, and tried criminal pleas; and also conducted jury trials in ordinary civil pleas, either taking the place of the sheriff, or more commonly associated with him. In default of the sheriff, or if he was a party in a suit, royal writs were regularly executed by coroners; and furthermore, occasionally they were employed by the crown to transact purely ministerial or administrative business, assisting or superseding the sheriff. Indeed throughout the thirteenth century the coroner acted as a check on the former. The coroner was representative not merely of the king but also of the people, being elected in the county court, from the county, and "with the assent of the whole county"; and being a man of substance and credit, and a knight, one of the original qualifications required being the knighthood,<sup>8</sup> was less liable to be oppressive and obnoxious to the people than the sheriff, who often bought his appointment from the crown, frequently lived in some other county, and generally regarded his office as an instrument of private gain. A survival of this historical relationship between the two offices is still exemplified, by the well known legal maxim that the coroner is the only officer empowered to arrest the sheriff.<sup>9</sup>

In England the coroner is appointed for life, or *quamdiu se bene gesserit*, for time of good behavior. In the United States, as we shall see later, the appointment is for a specified period of time, generally for two or four years. Coroners are exempt from serving offices which are inconsistent with their duties. They are also privileged from being summoned on juries, and from arrest while engaged in the execution of their duties.<sup>10</sup>

In England the coroner may appoint a deputy coroner to act during his illness or absence.

According to British law, a coroner can be removed from office only by decree of the High Court of Justice after conviction of extortion or misdemeanor, or by writ of the Lord Chancellor after proof of misbehavior or inability in office.<sup>11</sup> Similarly in the United States, in those states where he is appointed by the governor, he is responsible for his action directly only to the governor.

Coroners in England may logically be classified into four classes:<sup>12</sup>

First: Official Coroners. These are the Lord Chief of Justice and all the judges of high courts; who are coroners by virtue of their office, but never act as such.

Second: Franchise Coroners. These hold their appointment by virtue of ancient charters granted to special households or communities. Thus there is the coroner of the verge or the king's household; again, the wardens of the Stanneries of Cornwall may act as coroners; and, lastly, the Lord Mayor of London is a coroner, but does not act as such.

Third: Borough Coroners. These are appointed by the borough councils.

Fourth: The most important of all, the county coroners. The county coroners were elected from time immemorial by the vote of all the free-holders of the county. These elections, however, gave rise to so much scandal and abuse, that Parlia-

ment in 1888 by a clause in the Local Government Act decreed that in the future all county coroners should be elected by the county councils. This was a salutary reform, for the county councils generally exercise wise discretion and choose worthy candidates with both legal and medical qualifications. The county coroners as appointed and qualified by the Coroners Acts of 1887 and 1892 are essentially the coroners of to-day.

By the Coroners Act of 1887, the functions of the coroner are defined as follows:

Where a coroner is informed that the dead body of a person is found within his jurisdiction, and there is a reasonable cause to suspect that such person has died either a violent or an unnatural death, or has died a sudden death of which the cause is unknown, or that such person has died in prison, or in such place or under such circumstances as to require an inquest in pursuance of any act, the coroner, whether the cause of death arose within his jurisdiction or not, shall, as soon as practicable, issue his warrant for summoning not less than twelve nor more than twenty-three good and lawful men to appear before him at a specified time and place, there to inquire as jurors touching the death of such person as aforesaid. (Sec. 3 (1).)

Under this Act he is empowered to summon medical witnesses and order a post mortem (S. 21). If any person is found guilty of homicide the coroner shall commit him to prison for trial. He may accept in his discretion bail in case of manslaughter. Since the abolishment of public executions he must hold inquests on bodies of executed criminals. The duty to inquire into cases of treasure-trove is still present in the Act of 1887. In the United States this duty has been abolished, except in so far as it is the coroner's duty to take charge of the valuables found on unknown dead persons and to deposit them for safe-keeping in a proper public institution.<sup>13</sup> In the city of London by the City of London Fire Inquest Act of 1888, the coroner still holds inquests in cases of loss or injury by fire.

The Act of 1892 deals chiefly with the appointment and duties of deputy coroners in England. We cannot here go into a more detailed examination of the Coroners Acts of 1887 and 1892, but all those especially interested should read the excellently annotated edition of those Acts by Jervis.<sup>14</sup>

The most important function of the coroner, the function by virtue of which he possesses considerable magisterial powers, and through which he differs from all analogous officers on the European continent, is the holding of jury inquests.

"Inquest" or *inquisitio* is an interesting survival of a word which is associated with the birth of a new system of procedure, and which in mediæval England was a common generic term applicable to all forms of investigation, whether used for judicial or administrative purposes. There is good reason to believe, as pointed out by Gross,<sup>15</sup> that the coroner's inquest and coroner's jury, had an important bearing on the development of the modern trial jury. The coroner's jury in the thirteenth century consisted of representatives of the four neighboring *villatæ*, or townships, that is, the one in which the body was found and three others. Now the activity of these four townships was not confined merely to coroner's

At the appointed time and place, the jury meets, and the coroner opens the coroner's court and conducts the inquest. He summons the witnesses, swears them in, and gathers the evidence. The jury may ask the witnesses questions. Here, also, the pathologist or physician who has performed the post-

mortem, delivers his report. In all important cases the coroner furthermore has a member of the state's attorney's office at his side to advise him, and all evidence is taken down by a court stenographer.

Having heard the evidence the coroner summarizes the case and asks the jury to deliberate and return a verdict. Instances have occurred where coroners have unduly influenced the jury in their deliberations.<sup>22</sup> It is therefore customary for the coroner and all other persons to go out and leave the jurors alone. When the jury has agreed on the verdict, the foreman whom the coroner had previously designated, announces the decision. The verdict is then written down and signed by the coroner and each of the jurors on a special printed form as shown on opposite page. After that the coroner discharges the jury.

One inquest may be held on the bodies of several persons if they were killed by the same cause and died at the same time.<sup>24</sup>

The coroner being a judge, enjoys certain special privileges the same as other judges. Thus he is not liable for error or mistake.<sup>25</sup> He cannot be held for defamatory words used at an inquest.<sup>26</sup> He can turn anyone out of the room where the inquest is held.<sup>27</sup> He has the power of arresting and detaining the accused after the inquest (S. 5 (1)).

It is customary for the coroners in this city, for the good of the public, to make reports of the various cases they investigate to the police department, and they are required by law to make monthly reports to the police commissioners of all the cases coming under their jurisdiction. (Balto. City Charter (1898), S. 297).

It will be seen that the holding of a jury inquest is quite a complicated procedure, which takes considerable time and imposes a good deal of inconvenience on the jurors, and an additional expense on the State. The question, therefore, arises, when shall an inquest be held and when not? The decision on this point is left entirely to the discretion of the coroner, although the law broadly lays down the indications. According to the Public General Laws of Maryland:

No coroner shall summon or hold any jury of inquest over the body of any deceased person where it is known that the deceased came to his death by accident, mischance or in any other manner, except where the said person died in jail, or where there are such circumstances attending the death or case as to amount to a strong probability or reasonable belief that the deceased came to his death by felony.<sup>28</sup>

Unless, therefore, the coroner's preliminary investigation reveals facts concerning the death sufficient to create in his mind a reasonable belief that it resulted from some unlawful means, or unless the deceased died in jail, he is not justified to hold an inquest and impose an extra burden upon the jurors and the State.

Coroners have been criticised for holding too many unnecessary and expensive inquests,<sup>29</sup> and in the case of a coroner in Lancaster County, Pennsylvania, who sued to recover fees for an inquest in a case of death from paralytic stroke, the supreme court refused the payment, the opinion handed down reading as follows:

Where there is no ground for suspecting that death was not a natural one, it is a perversion of the whole spirit of the law to compel the county to pay for such services.<sup>30</sup>

The coronership is often regarded by the public at large and by a great many medical men as a sort of a sinecure. The coroner is supposed to draw his salary and have nothing more to do than hold an occasional inquest, say once or twice a month. This idea is due to the general ignorance on the part of the public concerning a coroner's duties. Although the conducting of jury inquests is the most important of his functions, that is but a small part of his work. It is the coroner's duty to investigate, or to use a technical term to "make inquiries" into, a large number of cases of death. The following classes of deaths must be all referred to the coroner and investigated by him, and the bodies cannot be buried without his certificate.

- I. **All violent deaths.** This includes homicides, suicides and accidents.
- II. **All sudden deaths,** whether violent or otherwise. By sudden deaths we generally understand deaths occurring after an illness of less than twenty-four hours.
- III. **All suspicious or unnatural deaths** from whatever cause, such as poisonings, drownings, burnings, still-births of unmarried women, deaths of infants of unmarried women occurring within a few days after their birth, etc.
- IV. **All deaths where there has been no attending physician.** Parenthetically, I may mention, that under this heading fall also the Christian Scientists.
- V. **Deaths in prison.**

In all the above cases the coroner has a right to and should insist, that they be brought to his notice, and not leave it to the discretionary judgment of the physician who may have been in attendance (if there has been one) as to whether he shall be notified or not. In cases of accidents or other violent deaths, the coroner should investigate all cases, even where the accident did not suddenly terminate life, but where the victim lived several days, and died afterwards from some complication brought on by the injury.<sup>31</sup> This opinion has been sustained by courts.<sup>32</sup> Perhaps some idea of the work done by coroners in this city may be gained if I will merely state that in the Northwestern District, the coroner has on the average at least about thirty and sometimes more cases of death to investigate or hold an inquest over in one month. In the Central and Northeastern Districts there are just as many and often more.

We have seen at the beginning of this paper that the coroner's office is well nigh a thousand years old. It is therefore not surprising that it has received its share of both praise and adverse criticism.<sup>33 34</sup> The commonest objection raised is that of the inherent incongruity of an office requiring a knowledge of law and medicine.<sup>35</sup> Such criticism is a platitude and quite unjustifiable, for medico-legal matters, from the very nature of their subject, demand a harmonious combination of legal and medical knowledge or experience;



whether they be dealt with by a single officer such as a coroner, or by two officials, such as the medical examiner and a lawyer in some states, is all the same. To abolish the office merely in order to divide the work between two specialists is in the words of Wyatt Johnston "an extreme measure and not actually called for."<sup>18</sup> As a matter of fact it would seem that a preliminary investigation by a properly trained medical man, such as a coroner should be, empowered to summon and examine witnesses under oath and followed if necessary by a subsequent inquest by an intelligent jury, is the best form of procedure. That this officer should preferably be a medical man stands to reason, for obviously the most important questions to answer are "how" and "in what manner," a person has come to his death; the questions "when" and "where" are not so intricate as to need great legal acumen.

We may draw, I think, an interesting analogy between the coroner and that other officer, whose calling is even older than that of the coroner, whose function is to watch over and preserve the life and health of the people, and the importance of whose position is beginning, even at this very time, even in this era of specialization, to be more and more appreciated—the family physician. It is the latter and not the specialist that knows best each and every member of the families entrusted to his care—their weaknesses, their private life, their relations to the outer world; and it is he who in emergency, in moments of anxiety and sorrow, can best take in the situation, can diagnose, advise, and bring relief. He, too, can best decide, if anything unusual has happened, and he is the one that can judge best, if expert help or specialists are needed. So, with the coroner. Being a man well-known in the community, a competent physician, versed in the rudiments of law, acquainted with the world at large—he can and will dispose most quickly and efficiently of all the ordinary cases; at the same time, if anything unusual or important should happen, he always can and will obtain all the expert aid he wants. Thus in this city the coroners always have at their disposal the hearty cooperation and assistance of an expert pathologist and a chemist on the one hand, and all the legal advice they desire from the state's attorney's office on the other.

But, just as the ordinary family physician is now-a-days expected to be acquainted to some extent at least with all the branches of modern medicine, and keep in touch with the latest progress and advances of his science, so ought the coroner to have at least a reasonable amount of medico-legal training. Speaking of the training of medical officers in forensic medicine, Prof. Dr. P. Dittrich, of Prag, says: we cannot be expected to know all, but

*Ein gewisses minimum ist man zu verlangen verpflichtet*<sup>19</sup>

and conscientiously speaking that minimum ought to be a "good deal."

What are some of the subjects that should come and do come under the head of coroner's duties? Perhaps I can review them best by discussing briefly six cases which happened to come under my jurisdiction within 48 hours last summer.

CASE I.—Was that of a dead infant—a "still-born" the mother called it. To investigate such a case carefully, a number of very important problems present themselves. In the first place it is necessary to determine if possible the age of the fetus; then it is well to know how long it has been dead. The question as to the cause of death is a very important one. It brings up the consideration of abortions and infanticide. Furthermore, if the birth was a natural one, was the child alive when it was born and died after delivery, or was it dead in utero? The latter point may be of great consequence in civil processes, in regard to legitimacy and inheritance.

CASE II.—A poor man living alone with strangers was taken sick and after a brief illness died, without having been attended by a physician. This case shows the importance of a post mortem examination in all obscure cases. Not knowing anything about the deceased, and not getting any history as to his past or to his illness, the question as to the cause of death is practically impossible to answer without the pathological examination. The problem of determination of personal identity is one of the most interesting, one of the most important, and one of the most difficult chapters of legal medicine.

CASE III.—A white woman went to church one Sunday night, and on her way suddenly felt "bad." She was taken to the nearest doctor's office, and there died in a few minutes. This is an illustration of the cases of "sudden deaths" mentioned above, which must be referred to the coroner. The cause of death in this case could be positively determined from the past history of the deceased. On inquiring into it, it was learned that she had been suffering from organic heart disease. The case illustrates the importance of a careful inquiry into the past history of a dead person, especially in cases like the present, where there is great objection to and no urgent necessity of making an autopsy. The coroner must often be able to make a correct diagnosis of the cause of death from the history of a case.

CASE IV.—A child was brought to one of the city hospitals suffering from the effects of drinking a can of lye. Lye poisoning is quite common among the children of poor negroes, and this is but an illustration of an unnatural death through poisoning. The case, however, brings up the very intricate and extensive subject of toxicology, a science by itself, but with some of the various points of which every medico-legal officer ought to be familiar.

CASE V.—A young man was found dead lying on the bed in his room with all doors and windows locked, and the gas jets turned on, evidently a case of suicide. Suicides, however, are often very difficult to differentiate from homicides; a very careful investigation of the environment and all the attending circumstances must therefore be made. Furthermore, this case brings us again into the field of toxicology—poisoning by illuminating gas. Again it is desirable to find out how long the body had been dead, which requires a knowledge, by no means easy to acquire, of the signs and phenomena of death, and of post mortem changes. Then again, if the suicide is a stranger, extreme ingenuity may be required to establish his identity. Furthermore, the motive for the taking of life touches upon the subject of sanity and insanity, all of which come within the province of legal medicine.

CASE VI.—A boy was brought to a hospital in an unconscious state. The mother stated that he was playing on a high express wagon, that he was pushed off by some party, and falling hurt his head. A doctor was summoned, who diagnosed the case as a concussion of the brain, and sent the patient to the hospital. The child died on the following day with the symptoms of meningitis; a lumbar puncture seemed to confirm the diagnosis. The X-ray specialist thought that there was a very fine linear fracture on one side of the skull. The autopsy, ordered by the coroner revealed a definite linear fracture of the skull, but on the opposite side of the head from that indicated by the X-ray man. There was general congestion of the brain, but no sign of meningitis. This case

illustrates, how difficult it is sometimes to determine the cause of death especially when two sets of symptoms are present. Some of the physicians were of the opinion that death was due to meningitis; others attributed it to a fracture of the skull. If a meningitis had existed at the time of the accident, it would have been of the greatest importance in a civil suit, for in one case death might have been due to an accident, in the other to natural causes. This case touches also upon the subject of wounds, their nature and classification, the evidence presented by them as to their causation, and their relation to death. I will not go into the consideration of criminal negligence and responsibility which this case raises.

These are but a few of the subjects with which a coroner ought to be familiar. Are all coroners acquainted with them? We must confess, too often they are not. That is why the office has come into disrepute, and that is why the nestor of our profession, Abraham Jacobi, in one of his addresses speaking of coroners in New York exclaims with his characteristic force: "

What is their preparation for that office? They are elected by the people at the tail end of the ticket, while their office should be one coming next to that of mayor and far above that of sheriff, with which the coronership is often classed.

Why and when are they nominated at all?—usually about or after midnight, when the nominating committee is bored and sleepy. Are the nominees good doctors, first-rate lawyers . . . ? Usually the men, with some praiseworthy exceptions, are but little known in their district, they furnish a surprise to the reading public, who wonder and submit.

And what are some of the subjects that should come and did come under the head of coronership? Let me mention a few: The exact knowledge of the signs of life, the changes caused by death, by no means an every day's easy task; the cause of death in the still-born or the premature child; the proofs and disproofs of infanticide; the explanation of sudden death in the very young. The discovery of poisons is one of the most difficult tasks of the chemist. The responsibility of physical defectives belongs to the coroner's domain—a murder may have been committed in the first attack of epilepsy; simulation must be diagnosed from actual disease, and the results of infectious diseases of the most common type often lead to crime. All this must be well understood to distinguish the sick person from the criminal, all this and much more belongs to the office of the coroner.

The trouble with the coronership in America is the trouble with so many other departments of our government. The laws are good; their administration and execution are often bad. We need not new laws, but a loftier conception and more conscientious execution of the old ones!

But already we note the signs of an awakening, and a brighter outlook for the future is before us.

As I conclude this paper, I cannot but recall a famous maxim from the Talmud:

לא ירומו של אדם מנבדו

אלא היא מנבדו את ירומו

"It is not the office that giveth honor to the man; it is the man that bringeth honor to the office."

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## DR. EPHRAIM McDOWELL, "FATHER OF OVARIOTOMY": HIS LIFE AND HIS WORK.\*

By AUGUST SCHACHTNER, M. D., Louisville, Ky.

During a visit to Germany in the summer of 1911, I talked with several Germans about Dr. Ephraim McDowell, and grew convinced that neither the man nor his work were as

thoroughly understood as they deserve to be. This discovery became my *chief* reason for investigating Dr. McDowell's life, and for my endeavor to prepare a clear presentation of him and his work.

In the present paper lack of time compels me to present the

\* Paper read before The Johns Hopkins Hospital Historical Club, December 9, 1912.

subject in a direct and concise form, foregoing in many instances details of circumstances and reasons for reaching and holding certain conclusions.

According to the family tradition, the ancestors of Dr. Ephraim McDowell emigrated from Scotland to North Ireland, during the Protectorate of Cromwell, about the middle of the seventeenth century.

Ephraim McDowell, the great-grandfather of Dr. Ephraim McDowell, fought in the English Revolution. At the age of 16 he was one of the Scotch-Irish Presbyterian defenders of Londonderry, during the troubles in 1688, and aided in resisting the besieging forces of James II in the memorable siege of 1689. His wife was Margaret Irvine, his first cousin. With his two sons, John and James, and his daughters Mary and Margaret, he emigrated to America, landing in Pennsylvania. It is believed that his wife died in Ireland. The date of his arrival in Pennsylvania, where he remained several years, is unknown, possibly, as thought by some, September 4, 1729. In Pennsylvania his son John, who was the grandfather of Dr. Ephraim McDowell, married the thrice-wedded Magdalena Wood, and it was here that Samuel, the father of Dr. Ephraim McDowell, was born, on October 29, 1735. In 1737 Ephraim McDowell, his son John, his son-in-law, John Greenlee, with his wife Mary McDowell Greenlee, moved by way of the lower Shenandoah Valley to what is now Rockbridge County, Virginia, near the present town of Lexington. They were the first three settlers in that region.

The great-grandfather of Dr. Ephraim McDowell died at the age of about 100. He lies buried in Rockbridge County, Virginia.

Capt. John McDowell, the father of Samuel McDowell, and the grandfather of Dr. Ephraim McDowell, fell in a battle with the Indians on Christmas day, 1743. He left three children, Samuel, James and Sarah. Samuel, the oldest, born in Pennsylvania, October 29, 1735, was the father of Dr. Ephraim McDowell. Two years later John McDowell moved with his family to Virginia. Samuel, as he grew up, received a good education for those times, one of his instructors being his relative, the distinguished Dr. Archibald Alexander. On the 17th day of January, 1754, in Rockbridge County, at the age of 18, he was married to Miss Mary McClung, daughter of John McClung and Elizabeth Alexander. Miss McClung, of Scotch parentage, was born in Ireland on October 28, 1735. Samuel McDowell and his wife Mary had 11 children born to them. When twenty years old he fought in the French and Indian War. He served under General Washington, and was present at the battle of Braddock's defeat. In 1774 he served as captain in Dunmore's War, and in the battle of Point Pleasant was an aide-de-camp to General Isaac Shelby, who afterwards became the first governor of Kentucky, and whose daughter later became the wife of Dr. Ephraim McDowell. Samuel was a colonel in the war of the Revolution, and with his regiment served under General Green at the battle of Guilford's Court House, and throughout Green's campaign against Cornwallis.

Preceding the Revolution, Samuel McDowell and Thomas Lewis represented Augusta County in the Convention of 1775

at Richmond, and protested against government by any ministry or parliament in which the people were not represented. They were delegated to address to George Washington, Patrick Henry, Benjamin Harrison, and other delegates from Virginia in the Continental Congress, a letter of thanks and approval of their course. In 1776 Samuel McDowell was a member of the Convention held at Williamsburg, Virginia, which instructed the delegates to the Continental Congress to declare the colonies free and independent.

He was appointed in 1782 by the Virginia legislature one of the commissioners to settle land claims in what was then a portion of Virginia, but afterwards became the state of Kentucky.

In 1783 he came as a surveyor with his family over the Wilderness Road, and took up his residence in Fayette County. In that year, at Harrodsburg, he, with two others, presided over the first court held in Kentucky. The next year he moved to Mercer County, in which Danville was situated. According to Collins, he was made president of all the early Kentucky conventions, nine in number, including the one that framed the Constitution of Kentucky. During his presidency in 1792, Kentucky was admitted to the Union.

In religion he was a member of the Presbyterian Church. He remained upon the bench until a few years before his death, and was known as Judge McDowell, to distinguish him from one of his sons, Samuel. After a long and useful life, during which he enjoyed the fullest measure of confidence and esteem throughout his state, he passed away, September 25, 1817, at the age of 82, at the residence of his son, Colonel Joseph McDowell, near Danville, Kentucky.

Dr. Ephraim McDowell was born November 11, 1771, in that portion of Augusta County, Virginia, that is now called Rockbridge County. He is generally referred to as of Scotch-Irish stock. Correctly speaking, he was born in the colony of Virginia, under the British flag, of Scotch parentage. Both sides of his house were Scotch. They emigrated to America by the way of, and after some residence in, Ireland. The Scotch-Irish reference in this, as in most other instances where it is employed, is misleading, and is based upon the residence in Ireland and not upon any mixture of Scotch and Irish blood. He was the ninth of eleven children, and the sixth son. When about 13 years of age, he moved from the place of his birth to the place of his future activity, Danville, Kentucky.

He received the best education that those early times and frontier conditions afforded, which, however, according to our present standard, might rightly be termed limited. Worley and James, who conducted a school at Georgetown, and later at Bardstown, were among his teachers. He also attended the Academy at Lexington, Virginia. His subsequent reputation as an athlete, while at the University of Edinburgh where he was successfully pitted by his class against an Irish professional in a foot race, lends color to the view that at school he was fonder of outdoor sports than indoor studies.

Later he studied medicine for two or three years with Dr.



Alexander Humphreys, of Staunton, Virginia, who was a graduate of the University of Edinburgh.

In 1793 and 1794, McDowell attended the University of Edinburgh. It is believed that while there he gave especial attention to anatomy and surgery. Apparently dissatisfied with the surgical lectures, or at least feeling a desire for more instruction in this line of work, he became a member of the private class of John Bell, who, in addition to being an able surgeon, was a clear and forceful teacher, and a man of charming personality. It is generally thought that from Bell's influence, together with his lucid lectures upon the diseases of the ovary and his statement that some day surgery would relieve those suffering from ovarian troubles, the seed sprung from which developed the operation of ovariectomy.

Indications justify the belief that he left Edinburgh without his degree, although some of his relatives claim that he secured it. He returned from there in 1795 and began the practice of medicine at his home in Danville where he remained until his death.

In 1817 the Medical Society of Philadelphia, the most distinguished of that time in this country, publicly recognized McDowell's ability, and in 1825 he received an honorary degree from the University of Maryland. This appears to be the first degree that was ever conferred upon him. Lunsford P. Yandell, Sr., suggests that this came through John P. Davidge, one of the founders of the University of Maryland, for Davidge was a friend and contemporary of McDowell at the University of Edinburgh.

Situated as he was, in a frontier city, favorably known and extensively connected, and with what was at that time unusual, a training in one of the best, if not the very best of the foreign universities, it is needless to say that an extensive practice covering what was then the entire southwest rapidly sprang up.

Hardly any anecdotes of his childhood or personal recollections of his manhood are known. He is described as erect and tall, nearly 6 feet, and inclined to corpulency, with a florid complexion and lustrous black eyes. He was a ready wit and fine conversationalist. In an unpretentious way, he was fond of music; he would sing English and Scotch songs with comic effect, accompanying himself with his violin upon which he performed with ordinary ability. He mingled freely with all classes of his townspeople, displaying the modesty and simplicity of a great man. He is said not to have used tobacco in any form, and to have been temperate in his habits. He was neat in person and invariably dressed in black, wearing a silk stock and ruffled linen.

He inclined to surgery; the medical side of his work he transferred as much as possible to his partner, and in his instructions to his pupils, he urged them not to rely too much upon drugs. His foreign training and Scotch origin explain his preference for Cullen and Sydenham in medicine, and Burns and Scott in literature. He was no writer; his only contributions to medical literature are said to be two reports in the *Eclectic Repertory* and *Analytical Review* upon his ovarian operations.

At the age of 31, he married Miss Sarah Hart Shelby, who

was then in her eighteenth year. She was the daughter of Governor Isaac Shelby, Kentucky's first governor. Six children were born to them, two sons and four daughters. Three of the children survived him. Through the influence of his wife, he became a member of the Episcopal Church. Several years before his death, he retired to his country home called Cambuskenneth, located about two miles from Danville, but did not give up the practice of medicine.

His death occurred while still in the full vigor of life. The illness began suddenly, while he sat in his garden eating strawberries. The chief symptom was great pain, followed by nausea and later by fever, which is said to have lasted fourteen days, when he died (possibly of an acute appendicitis). In his death, which, according to some, occurred on the evening of June 20, and according to others, June 25, 1830, in his 59th year, he preceded his wife ten years. They were both buried in the family burying ground, near Danville, at Travellers Rest, the home of his father-in-law. In 1872, Dr. John D. Jackson, of Danville, seconded by Dr. Lewis A. Sayre, started a movement which was completed through the Kentucky State Medical Society in 1879, and had, as its results, the removal of the remains of Dr. Ephraim McDowell and his wife, to Danville and the erection of a shaft over their graves.

On December 13, 1809, fourteen years after he began the practice of medicine, he was called to see a Mrs. Crawford, who lived in Green County, some 60 miles from Danville. She was thought to be pregnant and had exceeded her time. McDowell, after an examination, explained to her the nature of her condition and his proposed plan of relief.

Exactly what passed between McDowell and his memorable patient is mere speculation and will never be known. The operation at the time of its performance, received, considering its importance, comparatively little attention even from McDowell himself. An account of it was not published until about seven years later and then only after considerable urging on the part of his friends.

This much we know, that Mrs. Crawford yielded to McDowell's judgment and made the journey to Danville on horseback, it is said resting the tumor upon the horn of the saddle.

There is a tradition that McDowell's life was threatened by an angry mob for his rashness in performing the operation. This will never be satisfactorily proven or disproven. It seems, on reflection, reasonable to assume that this story has with time become exaggerated. McDowell was generally underrated by many and specially maligned by his enemies. He was held, however, by the greater part of his people to be easily the foremost man in medicine, and also considered a leading citizen in his community. Mrs. Crawford's evident entire willingness to undergo the operation is emphasized especially by the distance and difficulties under which she made the journey. No doubt the proposed operation was known to every one beforehand and in all likelihood, as is customary in small places, even to-day, where news is at a premium and where the tedium of the lives of the people is broken by their interest in their neighbors' affairs, there were comments of all kinds. In fact it is said that his nephew, Dr. James McDowell, whom he brought

up and who was his partner, made several attempts to dissuade him from operating and agreed only at the last moment to be present, and assist for fear of the damage he would sustain in his practice in the event of failure of the operation.\* There does not appear, however, enough ground upon which to base the story of an organized effort to do him bodily harm in the event of failure.

After the lapse of seven years following the first ovariectomy and at the repeated urgings of another nephew, William, and others, he was prevailed upon to prepare a report of the first three cases. This was forwarded in 1816 to his old teacher, John Bell, to whom it is believed he was indebted for the idea, but fell into the hands of John Lizars, owing to Bell's absence in Italy in quest of health.

Another copy was sent in the autumn of 1816 to Philip Syng Physic of Philadelphia, with a request that it be published if found worthy and this, like the first, received no attention.

His nephew, William, who was the bearer of the report to Physic then turned to Dr. Thomas C. James, who has passed into history as the modest, amiable and benevolent professor of midwifery in the University of Pennsylvania, and one of the editors of the *Eclectic Repertory*.

Professor James, who placed confidence in McDowell and his nephew, took the time to study and then communicate the report to his pupils, amid their applause, and later publish it in the *Eclectic Repertory* and *Analytical Review* (Vol. VII, 1817). The original report, which, we feel, in view of its importance and interest should be reproduced in full as far as least as it deals with the first case, is as follows:

In December, 1809, I was called to see a Mrs. Crawford, who had for several months thought herself pregnant. She was affected with pains similar to labor pains, from which she could find no relief. So strong was the presumption of her being in the last stage of pregnancy that two physicians, who were consulted on her case, requested my aid in delivering her. The abdomen was considerably enlarged and had the appearance of pregnancy, though the inclination of the tumor was to one side, admitting of an easy removal to the other. Upon examination, *per vaginam*, I found nothing in the uterus, which induced the conclusion that it must be an enlarged ovarium. Having never seen so large a substance extracted, nor heard of an attempt or success attending any operation such as this required, I gave to the unhappy woman information of her dangerous situation. She appeared willing to undergo an experiment, which I promised to perform if she would come to Danville (the town where I live), a distance of sixty miles from her place of residence. This appeared almost impracticable by any, even the most favorable conveyance, though she performed the journey in a few days on horseback. With the assistance of my nephew and colleague, James McDowell, M. D., I commenced the operation, which was concluded as follows: Having placed her on a table of the ordinary height, on her back, and removed all her dressing which might in any way impede the operation, I made an incision about three inches from the musculus rectus abdominis, on the left side, continuing the same nine inches in length, parallel with the fibers of the above-named muscle, extending into the cavity of the abdomen, the parietes of which were a good deal contused, which we ascribed to the resting of the tumor on the horn of the saddle during her journey. The

tumor then appeared full in view, but was so large that we could not take it away entire. We put a strong ligature around the Fallopian tube near the uterus, and then cut open the tumor, which was the ovarium and fimbrious part of the Fallopian tube very much enlarged. We took out fifteen pounds of a dirty, gelatinous-looking substance, after which we cut through the Fallopian tube and extracted the sack, which weighed seven and one-half pounds. As soon as the external opening was made the intestines rushed out upon the table, and so completely was the abdomen filled by the tumor that they could not be replaced during the operation, which was terminated in about twenty-five minutes. We then turned her upon her left side, so as to permit the blood to escape, after which we closed the external opening with the interrupted suture, leaving out, at the lower end of the incision, the ligature which surrounded the Fallopian tube. Between every two stitches we put a strip of adhesive plaster, which, by keeping the parts in contact, hastened the healing of the incision. We then applied the usual dressings, put her to bed, and prescribed a strict observance of the antiphlogistic regimen. In five days I visited her, and much to my astonishment found her engaged in making up her bed. I gave her particular caution for the future, and in twenty-five days she returned home as she came, in good health, which she continues to enjoy.

This report was met with indifference and incredulity on the one hand and ridicule on the other.

The original paper sent to Bell, which fell into the hands of Lizars, was published seven years after McDowell's report in connection with one of Lizars' failures, and it was this that awakened Europe and, through reaction, aroused America more than McDowell's own publication.

The second operation in 1813, four years after the first, was upon a negress. In this the ovary was exposed and incised, allowing a gelatinous substance and blood to the amount of about one liter to escape, but the ovary was not removed owing to the firmness of its adhesion to the *vesica urinaria* and *fundus uteri*. She recovered from the operation, had no more pain and was able to pursue her occupation. The third operation, and the last to be included in his first report, was performed May, 1816, or three years after the second. Like the second, it was upon a negress and in this case he removed a *scirrhous ovarium* weighing six pounds.

His second communication, also published in the *Eclectic Repertory*, embraced descriptions of his fourth and fifth patients, who, like the others, except the first, were negroes. The fourth was operated upon April, 1817. It was a *scirrhous ovarium* weighing five pounds. Although she made a recovery from the operation and it was the smallest of all, it gave him the most trouble at the time and was not as satisfactory in the end results as the others.

The fifth, who was operated upon May 11, 1819, had been tapped four times before the operation. Many adhesions were encountered. Sixteen liters of gelatinous fluid were discharged from the tumor and abdomen. She died of peritonitis on the third day. The tumor was a dermoid cyst.

These were the only cases that McDowell reported; the exact number of these operations he performed will never be known. Samuel D. Gross collected three additional cases, all white, making eight in all, four in white and four in negro women. Five operations were complete and three were incomplete. Of

\* In McDowell's own account of the operation he says, that his nephew, James McDowell, did assist him.

the five complete operations, there were two in white and three in negro women, with one death among the latter, the mortality of the completed operations thus being 20 per cent. William, his nephew and also at one time a partner, is the authority for the statement that his uncle performed the operation in all 13 times.

McDowell's surgery was not confined to that of the ovary. He performed lithotomy 32 times without a death. One of his lithotomy cases, James K. Polk, later became president of the United States. He operated for hernia and performed all the operations known in his time.

After a careful search the writer has been unable to find sufficient evidence to justify the belief that McDowell ever performed Cæsarean section or that he ever returned to Europe after leaving the University of Edinburgh. By preference he operated on Sunday mornings.

Considering the importance to humanity of McDowell's work, he has been overlooked to an unpardonable degree, but what must we say when we come to that brave woman, Jane Todd Crawford, who successfully balanced her heroism against McDowell's genius and thereby joined with McDowell in emancipating countless millions of human beings of all nations and creeds in time to come, from a terrible condition from which a miserable death alone supplied the avenue of escape.

Pearlee in 1870 estimated that McDowell had added 30,000 years to the active life of womanhood in the 30 years prior to 1870 in the United States and Great Britain alone through the operation of ovariectomy. This in itself, would be quite enough to entitle Ephraim McDowell and Jane Todd Crawford to the lasting gratitude of humanity.

McDowell's operations, by demonstrating to the world the feasibility and safety of entering the abdominal cavity, became the cornerstone of abdominal surgery. To estimate even approximately at present the thousands of human beings that are annually saved and the countless hundreds of thousands of years that are annually added to human life through abdominal operations, would be a task well nigh superhuman. Abdominal surgery has reached such proportions that ovariectomy is but one of its smaller divisions, and when we think that even this bids fair to be extended and still further improved, we begin to realize the priceless gift and the enduring obligation that humanity owes to Ephraim McDowell and Jane Todd Crawford.

For more than a century the heroine of this story has passed from one writer to the next as Mrs. Crawford, of Green County. No one seems to have thought it necessary to establish her identity that she might take her proper place in history.

After an investigation fraught with many difficulties, extending over many months, involving an enormous correspondence and assuming at times a discouraging outlook, I feel justified from the records in my possession, in presenting the following history of her:

Jane Todd Crawford, who richly deserves to share with McDowell the honor and glory of an international memorial for her heroism, was born in Rockbridge County, Virginia. She was the sister of Samuel Todd, of Frankfort, Kentucky.

Thomas Crawford and his wife, Jane Todd Crawford, with Thomas Mitchell, who in 1768 in Virginia had married Rachael, the sister of Thomas Crawford, moved to the waters of Caney Fork, nine miles southeast of Greensburg, arriving there November 5, 1805.

It must be remembered that Kentucky was still largely a wilderness and, owing to Indians and other dangers, emigrants moved about during the early periods not singly, but in groups. This was four years before Mrs. Crawford was operated upon. There is a record to show that Thomas Crawford and his wife, Jane, transferred to John Motley, 427 acres of land for \$1900, "cash in hand," December 8, 1810, one year after the operation. The land was afterwards known as Motley's Glen.

Five children were born to them, Hon. Thomas Howell, Crawford, who was mayor of the city of Louisville in 1859 and 1860, Rev. James Crawford, a Presbyterian minister, Samuel Crawford, Alice Craig Crawford, who married William Paul Brown, and a daughter who died in infancy. Dr. Samuel D. Gross has proven conclusively that Mrs. Crawford did not give birth to a child after the ovariectomy.

As the daguerrotype camera was not introduced into the United States until 1839, it is not reasonable to suppose that any photograph was ever taken of her and in all likelihood no portrait of her was ever painted. All efforts to procure what would seem a trustworthy description of Mrs. Crawford, and more details germane to the operation, have so far failed.

There is a tradition in the Mitchell family that McDowell made no charge for the operation, but that Mr. Crawford presented him with an honorarium so large that, considered in the light of that period and the contracting parties, it is out of reason to suppose the story credible, and is mentioned simply as one of the many errors and traditions that confronted us in our search.

The story of Jane Todd Crawford's subsequent movements, her death and the discovery of her grave which had been forgotten for about a century, is akin to a romance, but entirely too long for the present paper. Stripped of its details, a long search and an extensive correspondence brought the writer in touch with Mr. J. K. Mitchell, a lawyer of Osborne, Kansas, and a grandnephew by marriage of the heroine. Mitchell's vigorous efforts resulted in enlisting the aid of the Rev. J. H. McArthur, a Presbyterian minister of Sullivan, Indiana, who discovered the grave in the Johnson Cemetery ten miles northwest of Sullivan.

Since the family bible, in which the family records were kept, was burned during the fire that destroyed the house of Rev. James Crawford, it is practically impossible to determine her exact age. The date of her death has been given variously as 1841, 1842 and 1843. The inscription on her tombstone reads:

JANE CRAWFORD

Died

Mar. 30, 1842

Aged 78 years

Blessed are the dead who die in the Lord.

According to this she survived the operation 33 years.



In the spring of 1912 the writer started a movement to preserve and memorialize the house in which McDowell lived and performed the ovariectomy.

The importance of rescuing this historic landmark situated in what is now the questionable quarter of Danville, and used as a negro boarding house, is too plain to require more than mere mention.

With this end in view, the writer addressed the Kentucky State Federation of Women's Clubs at their annual meeting at Mammoth Cave, May 29, 1912, and urged them in view of being the first beneficiaries of McDowell's work, to unite in saving this structure. He said in part:

If benefits to the human race are to be the standard by which we measure the usefulness and importance of a life, I am prepared to defend the statement that the importance of Dr. Ephraim McDowell's life overshadows that of either Washington or Lincoln, and that the house in Danville in which the ovariectomy was performed, should be more sacred not only to an American, but to the entire human race, than any other structure upon the whole American continent.

It has been fashionable for centuries to ignore the real benefactors of the human race, and to rush madly forward with monuments and memorials to statesmen and especially military leaders. This is a remnant of feudalism that is still in us. It is a legacy from the time when might was right even in smaller matters, as it still is to a degree in international matters, when we, more fondly than we do to-day, worshipped power and pomp at the expense of equity and reason. I do not wish to be understood as detracting from the statesman and the warrior, but I do wish to point out the benefits of the work of such a man as Ephraim McDowell as compared with the very greatest statesmen and military leaders. The moulding of a nation, the advancement of a particular people by a wise statesman, and the leadership of a successful army in a just cause, are matters that do not admit of any division of opinion. Since, however, many statesmen are forcible but not wise, and many military leaders brave and daring in an unjust cause, it is obvious that both harm and good are equally dispensed by these two popular idols. And even when the statesman is wise, and the military leader is fighting a just cause, they affect but one people and that they affect perhaps for one period, quite enough to justify their activities I will admit, as we all must.

Compare, however, this with Ephraim McDowell, whose life has affected all people. When he, for the first time on December 13, 1809, performed, before the time of anaesthetics, and without trained assistants and the usual conveniences that to-day are considered as almost indispensable, the operation of ovariectomy, he conferred upon womanhood in particular, and mankind in general, a benefit as great as any that has ever been conferred upon the human race in this or any other country and in this or any other age.

I am sure that no one will for a moment, dispute the magnitude of this gift to humanity, but I am not sure as to how many of us can really measure the greatness of this deed.

Since women were the first beneficiaries of his work, it seems entirely natural for the women of Kentucky to rescue the house in which this memorable deed was performed and which has added to the honor and glory of Kentucky more than all her other achievements combined, great as they are.

When this is accomplished, there should be an international movement to erect a joint monument befitting the services to the memory of Dr. Ephraim McDowell of Danville, and Jane Todd Crawford.

I am here to make an appeal to you to unite in rescuing from

oblivion, what should be the most cherished and sacred structure in the entire Republic.

Even though the house should by some misfortune be destroyed, the spot should be memorialized. One feels like saying that it will be akin to savagery to ignore the spot where this deed immeasurable for its good, was consummated.

The appeal was favorably acted upon by the Kentucky State Federation of Women's Clubs. With commendable promptness a memorial committee was created. The writer made a number of efforts, some before and many during the half year following this action by the Federation, to persuade the owner of the building to place a valuation upon the same.

Although a man in affluent circumstances, he has resisted all entreaties towards placing a price upon the structure. As to whether John Gill Weisiger, the present owner, will ever be willing to sell this structure, that this shrine that spells more than volumes can describe, can be memorialized, that is a question that time alone can answer.

NOTE.—Since reading this paper before the Johns Hopkins Hospital Historical Club, a letter has been received from Mr. John Gill Weisiger offering to sell the house for \$10,000, the offer to remain in effect for five days. The price has been considered as being considerably higher than expected, but we hope that the Kentucky Federation of Women's Clubs who have created a McDowell Memorial Committee will be able to secure this house, and keep it as a memorial to Dr. Ephraim McDowell and Mrs. Crawford.



FIG. 1.—The McDowell Coat of Arms.

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FIG. 2. Dr. Ephraim McDowell. From a portrait in possession of his granddaughter, Mrs. William M. Irvine, Richmond, Ky.



FIG. 3.—Dr. McDowell's present burial place in Danville, to which his remains were removed in 1879 through the efforts of the Kentucky State Medical Association.







FIG. 1.—Premises and rear of house in which he performed the first ovariomy, showing the slovenly condition.



FIG. 2.—The house in which Dr. McDowell lived and performed the first ovariomy, showing the present character of the street.



FIG. 3.—Dr. McDowell's first burial place in the family burying ground at Travellers Rest, the homestead of his father-in-law, Gen. Isaac Shelby. The grave, as indicated by the arrow, was just beyond the slab seen in the center of the picture.

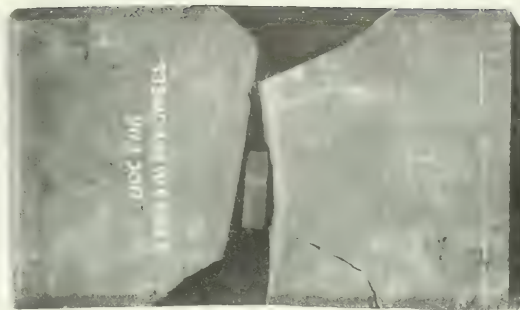


FIG. 4.—The remaining fragments of the slab that covered Dr. McDowell's first grave, by permission of Isaac Taylor, Esq., Shelby City, Ky. The inscription was brought out by brushing it with whitening.



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## NOTES ON NEW BOOKS.

*Surgery and Diseases of the Mouth and Jaws.* By VILRAY PAPIN BLAIR, M. D. Illustrated. \$5. (St. Louis: C. V. Mosby Company, 1912.)

Within a very brief period several works on this specialty have appeared, so that any surgeon desiring to make a thorough study of these conditions will have no difficulty in learning what are the best measures to employ. Blair's work is a good one for the specialist to have on his shelves; it covers the ground in a satisfactory manner. He shows how much can be done to improve a deformity, such as a receding chin, but it is to be hoped that further studies will enable the surgeon to perform less disfiguring operations in certain cases than is now possible. The progress along these lines has been great, but there is need of still more work in this branch of surgery, before the results will be as good as they ought to be or compare with those obtained in other surgical fields. This book will serve as a valuable stepping stone in that direction.

*Text-Book of Anatomy and Physiology for Nurses.* By ELIZABETH R. BUNDY, M. D. Second Edition Revised and Enlarged. Illustrated. \$1.25. (Philadelphia: P. Blakiston's Son & Co., 1913.)

The author says that the scope of the second edition of her text-book of Anatomy and Physiology for Nurses has been extended to include more definitely the subject of physiology. Her endeavor has been so to associate the consideration of the structure and functions of the various parts of the body that a com-

prehension of their anatomy and physiology may be simultaneously attained. Dr. Bundy has written the anatomical portions of her work very completely and in a manner calculated to be easily comprehended by the classes her volume is intended to reach. It is clear and not too much overburdened with detail. There is, however, an almost complete neglect of the histological structure of the body tissues.

That portion of the book—fully one-third the volume—given to the consideration of bone and muscle is very complete and well illustrated. The so-called "clinical and obstetrical notes" are always of interest and of practical significance.

The notes on physiology in this section though good are extremely brief.

The whole subject of the alimentary tract together with the consideration of foods and their digestion is rather too much condensed. This is also true of the respiratory system and the kidneys. The circulatory and nervous systems are very thoroughly and well discussed—especially from the anatomical standpoint.

The section on regional anatomy is admirable and very practical. In conclusion one might say that as an anatomy the book is excellent but as a physiology it falls far short of the ideal.

*Practical Cystoscopy.* By PAUL M. PILCHER, M. D. Illustrated. \$5.50. (Philadelphia and London: W. B. Saunders Company, 1911.)

Pilcher's Cystoscopy does not fill a long-felt want, but can be safely recommended to students. The author divides his work into seven parts: 1. The technic of cystoscopy; 2. The diseased



bladder; 3. Diseases of the prostate; 4. Diseases of the ureter; 5. The functional activity of the kidneys; 6. Diseases of the kidneys; and 7. Therapeutic uses of the cystoscope. It covers much ground as can be judged from these headings, but the ground is only lightly worked over.

This book is bigger in form than it should have been—the print is unnecessarily large and the margins far too wide. Had it been cut down to a reasonable shape and size it would have been more welcome and could have been produced more cheaply. There are a number of needless illustrations, and some of them are of poor quality, but others are excellent.

*A Text-Book of Pathology for Students of Medicine.* By J. GEORGE ADAMI, M.D., etc., and JOHN McCRAE, M.D., etc. Illustrated. \$5. (Philadelphia and New York: Lea & Febiger, 1912.)

The authors of this excellent volume state that it is to be regarded not as an abbreviation of their larger book, but as a new work with a somewhat different purpose. The general style of treatment is similar to that of the "Principles of Pathology," and represents an effort, aimed confessedly at the medical student, to present the facts and phenomena of pathology. These facts and phenomena are compared to bricks, and it is suggested that we must concern ourselves, not only with the raw materials, but with the plan and uses of the completed structure to be built from them.

The division is made into general and special pathology. The section on general pathology covers approximately 330 pages of the 708, and includes chapters on inflammation, the progressive and regressive tissue changes, and tumors, which are authoritative in character.

In the part devoted to special pathology, the treatment of the cardio-vascular system may perhaps be singled out for its especial excellence.

Amongst the introductory material may be found some innovations; for there are discussions of histology, physiology, immunity, the Mendelian law, etc. Teratology is fully covered, and Dr. Adami's ingenious classification of tumors is the one used.

The publishers' work has been well done, the type and illustrations being clear and satisfactory.

There can be little doubt that this is the best text-book in English at the present time, and it is to be recommended to the student of pathology.

*A Reference Handbook of the Medical Sciences.* Embracing the Entire Range of Scientific and Practical Medicine and Allied Science. By various writers. Third Edition, Completely Revised and Rewritten. Edited by THOMAS LATHROP STEDMAN, A.M., M.D. Complete in eight volumes. Volume I. Illustrated by numerous chromolithographs and 611 fine half-tone and wood engravings. Nine hundred and thirty-six pages. (New York: Wm. Wood & Co.)

Since the first appearance of this valuable handbook in 1885 the advance in medicine and allied sciences has been so great and so rapid that there is much in the first volume of the new edition which was not dreamed of more than twenty-five years ago. In all sciences there has been immense progress during these years, but perhaps in none have there been such revolutionizing discoveries as in medicine, and this makes a new edition of this work at this time especially acceptable to the profession. The second edition appeared more than ten years ago, and is now in measure out of date. The number of pages in the new volume are 928, eighty more than in the first edition, and whereas the original volume ran from "Aac to Cat," the new one includes only words from "Aac to Bac." This shows in part how many new articles there are, and also indicates that many of the articles are much longer now than they were. There

is some difference in the arrangement of the articles, for instance, in the first volume appeared "Anus and rectum: Diseases of." To-day the title reads "Anus: Diseases of the. See Rectum and anus: Diseases of the." There will doubtless be many such changes, and when the entire edition is published it will make but little difference to the reader, and is only noted to show that encyclopedia makers have various methods for cross-references, methods which naturally will not approve themselves to all readers.

Some of the articles are accompanied by longer or shorter bibliographies. There seems to be no method in this and the references are not, throughout, printed alike; that is in one article titles will be abbreviated, in others, given in full; and the method of noting the volume and page does not always agree. Except as regards appearance this is a point of small importance, but we believe there should be some system as to the introduction or omission of bibliographies. A severer reflection is that some of the references are very old, and indicate either that the article has not been revised or that the author has been careless in not adding more modern ones.

This applies also to the use of illustrations, about which there seems to be no general rule. Many of these might have been improved especially the colored ones, which do not appear to us satisfactory, in view of the excellent color reproduction which is now possible. In some instances old illustrations have been entirely omitted, and new ones take their place.

The first volume promises well and we doubt not that the handbook is going to be a most valuable addition to our medical libraries and that it will be heartily welcomed by the profession. The difficulties of the undertaking are very great, and no encyclopedia can be perfect or please everyone, but we are sure that under the editorship of Dr. Stedman this work will be an honor to him, and thus to the publishers as well.

*The Illness and Death of Napoleon Bonaparte.* By ARNOLD CHAPLIN, M.D. 70 cents. (London: Hirschfeld Brothers, Ltd., 1913.)

This book should be of universal interest,—to students and admirers of Napoleon, as it is an accurate description of the illness which closed a remarkable career,—to the medical profession as it clears up certain important points in regard to diagnosis and treatment,—and to the laity, because it is written in such a way as to be easily understood. In dealing with his subject, the author discusses in detail the history of the illness for the three years prior to death, the results of the post-mortem examination, criticisms of the diagnosis and treatment, and in conclusion sums up the entire case. In an appendix is given a biography of each of the physicians in attendance upon the distinguished patient while in St. Helena, a short account of the specimens in the museum of the Royal College of Surgeons of London, and of the exhumation of Napoleon in 1840. The book is a fair and just criticism of the faulty diagnosis and treatment, written from an impartial standpoint.

*Modern Methods in Nursing.* By GEORGIANA J. SANDERS, Formerly Superintendent of Nurses at the Massachusetts General Hospital, Boston. Illustrated. \$2.50 (Philadelphia and London: W. B. Saunders Company, 1912.)

This is a very comprehensive work of over 800 pages, and one which is sure to prove acceptable to many nurses, since it covers the ground so thoroughly. It is divided into 24 chapters. Miss Sanders takes up first beds and bedmaking, then baths and packs, local applications, with enemata, enterocolysis, etc. Then follows a chapter on the temperature, pulse, respiration and charts. Observation and examination, examination of vomitus, etc., bandages and splints, medicines, and poisons are the head-

ings of other chapters. Elementary bacteriology and theories of immunity are discussed in 50 pages. This is followed by eight chapters on surgical conditions. Symptoms and conditions frequently met with, three chapters on food, and one on the head nurse and ward management practically complete the book, except for a brief appendix on recipes, the index and introduction. There are numerous points to which exception might be taken, but they are not of vital importance and so can be passed over, without further notice except to draw attention to the fact that training of nurses varies largely in the different schools and that what are taught as the best methods of procedure in certain cases are not so considered by others. This remark is also applicable to what should or should not be taught nurses, and on this point also there is room for difference of opinion with Miss Sanders in some instances. None the less her book is one of the best that has appeared, for her instruction is reliable and serviceable.

*The Surgical Clinics of John B. Murphy, M.D. Volume II. Number 1. (Philadelphia and London: W. B. Saunders Company, February, 1913.)*

"Open Treatment of Fractures," "Fracture and Luxation of Neck of Humerus" and "Tuberculosis of the Knee; Arthrodesis" are some of the most noteworthy "Clinics" in this volume. They are well illustrated by X-ray and other photographs. The other "Clinics" are shorter and not so abundantly illustrated, and yet while all will be valued by the author's followers, we cannot but question the importance of the publication of some of them.

*Diseases of the Skin.* By WILMOTT EVANS, M.D., B.Sc., F.R.C.S. (Univ. of London Press.)

It is rather difficult to understand why the publishers felt that there was a need for a text-book of this character, in view of the overabundance of the supply now on the market.

The most successful works on diseases of the skin, are those that combine a short but clear description of the symptoms encountered, with numerous illustrations, from good photographs of well selected cases, which have lost but little in their reproduction.

In this book the text can be criticised favorably, but the illustrations leave much to be desired. They are too few, not well selected, and have reproduced poorly. With only 32 pictures, four are used to show only one type of syphilis, the ulceration. One of the illustrations of ichthyosis is not typical of that disease, and could more appropriately represent an eczema or pellagra. That of lupus certainly looks like a crusted eczema. It is also rather peculiar, in a text-book on skin diseases, to give photographs of plants which may cause a dermatitis, without showing the disease caused by them; yet two, of the 32 illustrations, are of the primrose and poison ivy, but dermatitis venenata is not represented.

It is to be hoped that the second edition will evince more care in this most important feature of a text-book on diseases of the skin.

*Diseases of the Eyes.* By C. DEVEREUX MARSHALL, F.R.C.S. (London: University of London Press, 1912.)

Very little need be said about this book. It is similar in every way to several other text-books which are practically syllabi of larger text-books. In the main, it is the opinion of the reviewer that abbreviated text-books are not of much value, and no exception would be made in favor of the present volume. No light is thrown on mooted subjects, and it is questionable whether some subjects are discussed with sufficient fullness to satisfy State Boards of Medical Examiners. Furthermore, some common, yet

important, subjects are omitted, such as vernal catarrh, transient episcleritis (Fuch's hot eye), superficial punctate, keratitis, Parinaud's conjunctivitis, etc.

In a number of places the author, as if in a hurry to close the discussion, makes statements at variance with accepted facts. We note this when he states that "Vesicular keratitis seldom occurs except in degenerated eyes," and also, when, on the subject of Tobacco Amblyopia, the following is met with—"When above directions are carried out, the sight will be *entirely* restored." The "Eye Signs" of Tabes and exophthalmic goitre are not even mentioned in its pages, nor is the Calmette tuberculin reaction spoken of, so that even if examined from the standpoint of the student or general practitioner, for whose use the book is intended, as indicated in the preface, the present volume is inadequate.

B. B. BROWNE, JR.

*Diseases of the Eye. A Manual for Students and Practitioners.* By J. HERBERT PARSONS, F.R.C.S. Second Edition. \$4. (Philadelphia: P. Blakiston's Son & Co., 1912.)

This is the second edition of this text-book. It should be found a fairly satisfactory book for the beginner in the study of eye diseases, for it covers the whole subject, including a short résumé of the anatomy and physiology. A too positive dogmatism is, at places noted in its pages, but the main points are covered with a fair degree of fullness and accuracy. For the clinical worker this book would have less value since the suggestions offered for the actual management of eye cases are rather vague and indefinite.

B. B. BROWNE, JR.

*The Anatomic Histological Processes of Bright's Disease and Their Relation to the Functional Changes.* By HORST OERTEL. Director of the Russell Sage Institute of Pathology, New York. (Philadelphia and London: W. B. Saunders Company, 1912.)

The problems underlying nephritis are so complex and there is so much difference of opinion among the best workers as to the fundamental changes in the different forms of nephritis that such a piece of scholarly work as Oertel's is welcome and deserves serious consideration. It is an important addition to the immense literature of the subject, and one that other workers along similar lines cannot afford to overlook. We regret the use of the term "Bright's disease," however, for it is vague and all scientists do not use it with exactly the same signification—this criticism only applies to the title and not the body of the work, in which he discusses mainly degenerative and exudative nephritis. The work is finely illustrated and students will find it abundantly worth their while to read it with care.

*Glycosuria and Allied Conditions.* By P. J. CAMMIDGE, M.D. \$4.50. (London and New York: Longmans, Green & Co., 1913.)

The appearance of such a book at a time when our views of carbohydrate metabolism are in such a chaotic state, is most apt. These are the days of close co-operation between the diagnostician, internist and laboratory worker: mistakes, hasty conclusions, and consequent errors in judgment made by one, become harmfully effective through the others. Perhaps no commoner error is made than that which assumes any urinary reduction as due to glucose; and the individual thus doomed to the diabetic verdict becomes further the victim of some rule of thumb treatment, in no way in keeping with his metabolic conditions. The author has tried in this volume of 450 pages to make such errors impossible.

After a short chapter dealing in a general way with the properties and physiology of carbohydrates, there follows an exhaustive

and practical discussion of the detection and estimation of sugars occurring in the urine and blood, as well as of the so-called "acetone bodies," total nitrogen and ammonia: the section is specific as to the relative merits and fallacies of the tests, and includes a discussion of substances other than sugars which may cause reductions: the list could be further amplified.

The chapter on experimental glycosuria is a résumé of work done since the famous picture of Claude Bernard: proper emphasis is placed upon the close relationship now known to exist between the various ductless glands and the control of sugar metabolism: the observations of Lepine, Falta, Eppinger and Cushing are certainly stimulating, since they tend to show that "glycosuria is not a disease, but a symptom common to many pathological conditions."

Alimentary and transient glycosurias, their causes and diagnosis precede the 190 pages devoted to a detailed discussion of true diabetes mellitus, its urinary findings, clinical symptoms, complications of the disease, its pathological basis, and the methods at hand for its early recognition: the *raison d'être* of many common subjective complaints is excellently and tersely described.

Through a concise review of normal metabolism the author makes clear the altered conditions in diabetes and the all essential factor in successful treatment, namely, individual study: he gives in detail the methods used by him in determining the proper dietetic régime: they differ in no essential details from those of von Noorden, and are perhaps not as clear or easy of application: the rational of various drug and glandular therapies is reviewed in the light of our modern pharmacological knowledge. The concluding three chapters deal with the subjects of leucosuria, lactosuria, pentosuria, alkaptonuria, and diabetes insipidus, the book ending with an admirable appendix devoted to a more minute and chemical consideration of the reactions of carbohydrates and allied bodies.

The book is readable, viewed both from the author's style and printer's presentation of the matter: typographical errors, if present, are remarkably few: an appropriate bibliography is given at the end of each chapter, a method highly to be commended; the index alone can justly be criticised from the standpoint of efficiency. The reviewer unhesitatingly recommends the book to consultants, practitioners, and students, as the best work of its kind in the English language. S. R. M.

*Malaria: Cause and Control.* By WILLIAM B. HERMS, M.A. Illustrated. (New York: The Macmillan Company, 1913.)

This small book is the result of the author's work in attempting to rid California of mosquitoes and is an excellent guide for other communities pursuing the same task. Mr. Herms has probably had greater experience in the controlling of malaria than any one else in the country and has written an admirable treatise. He covers all the essential points which need consideration, and has gathered a lot of material which is unusual but of distinct usefulness as showing how to go about the work. This book is really an important and valuable contribution, and we wish there were similar ones treating in an equally striking and appropriate manner some of our other common diseases—*ea.*, typhoid.

*Ophthalmic Surgery.* By DR. JOSEF MELLER, Vienna. Edited by DR. WILLIAM M. SWEET. Illustrated. Second Edition, Thoroughly Revised. \$3.50. (Philadelphia: P. Blakiston's Son & Co., 1912.)

This is the second edition of this work. The author describes the operative procedures which have been adopted in the eye clinic of Professor Fuch of Vienna. Quite a considerable portion of the text is given to a description of lid operations, which, as a rule, every operator modifies, more or less, to suit himself and

the particular case at hand. The description of the standard operations for cataract, glaucoma, and the enucleation of the eyeball, etc., are quite satisfactory. An abundance of well drawn pictures accompany the text. B. B. BROWNE, JR.

*Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India.* (Calcutta: Superintendent Government Printing, India, 1912.)

No. 57. *Studies on the Flagellates of the Genera Herpetomonas, Crithidia and Rhynchodomonas.* By CAPTAIN W. S. PATTON, M.B., etc. Price 1/2.

No. 58 and 59. *Studies on the Mouth Parts and Sucking Apparatus of the Blood-Sucking Diptera.* By CAPTAIN F. W. CRAGG, M.B., etc. Price 1/- and 1/11.

The subtitle of Captain Patton's paper is The Morphology and Life History of *Herpetomonas Culicis*,—Novy, MacNeal and Terry, and his study is therefore of special interest to a few students in America as the parasite found in India is probably identical with that found in this country. This memoir and the two by Captain Cragg are important as they help us to a more accurate knowledge of the ways in which diseases are transmitted. They are purely scientific and therefore will appeal to but a special class of workers to whose attention we are glad to call them.

*The Hunterian Lectures on Colour-Vision and Colour-Blindness.* By PROFESSOR F. W. EDRIIDGE-GREEN, F.R.C.S. (Eng.). \$1.50. (New York: Paul B. Hoeber, 1912.)

The material in this work is somewhat old, being delivered in the form of lectures in February, 1911. The views are speculative, and the author's ideas may have changed by this time.

B. B. BROWNE, JR.

*Systematic Case-Taking.* By HENRY LAWRENCE MCKISACK, M.D. \$1.50. (New York: Paul B. Hoeber, 1913.)

To internes or house-officers who have not been well instructed in writing histories of patients, the study of this small volume should prove most helpful. It is an excellent guide, compact and concise. The author has divided his matter into nine chapters: 1. Preliminary enquiries. 2. General examination. 3. The thorax. 4. Respiratory system. 5. Circulatory system. 6. Blood. 7. The abdomen. 8. Examination of the urine. 9. Nervous system. The fault with most case-taking is that no system is followed, and the history naturally becomes a jumble as the clinical clerk jumps from one organ to another, and there is no sequence in his development of the patient's history and condition. A student who makes a habit of taking his histories systematically will find it an immense help to him in all his work. It is an evidence of orderly thought and a well developed case history leads up far more precisely and accurately to the correct diagnosis than any other. Snap diagnoses may be correct, but they are the result of bad training and have an evil influence on the student's mind. This manual should serve an excellent end in teaching students how to go about their work, and in developing in them good methods of study. We commend it heartily.

*Surgery: Its Principles and Practice.* By Various Authors. Edited by W. W. KEEN, M.D., etc. Volume VI. Illustrated. (Philadelphia and London: W. B. Saunders Company, 1913.)

Between 1906 and 1909 this surgery was published in five volumes. To bring it as nearly as possible up to date this supplementary volume has been added. With but very few exceptions the original authors have described the advances made in the special branch of surgery previously written on by them. Seventy chapters, of a little over 1000 pages altogether, covering the whole



field of surgery, have thus been contributed by 61 physicians. The longest chapter of nearly 100 pages is in the surgery of the female genito-urinary organs, and we question whether the advances made in this branch of surgery justify a chapter so much longer than any other. Important surgical developments since 1909 embrace the treatment of cancer by fulguration, new methods of anæsthesia, the use of salvarsan, the opening of the thorax, operations on the hypophysis, etc., all of which are noticed in this volume, which makes a valuable addition to the system, and both Dr. Keen and the publishers are to be congratulated on having so successfully completed the original undertaking. The profession will be grateful for this final volume which makes the surgery as nearly perfect as it can be. That the editor should have succeeded in getting all the original writers to contribute these additional chapters shows the warm interest they took in the work, and their justified feeling that the surgery was a success and heartily appreciated by American surgeons.

*International Clinics.* Twenty-third Series. Volume I. (Philadelphia and London: J. B. Lippincott Company, 1913.)

More than a hundred pages of this volume are given to an interesting review of the progress in medicine during the year 1912. The article has been carefully prepared by Drs. Cattell and Johnson. A couple of noteworthy clinics are by Rugh and Abham—the former reports ten cases of Pott's disease of the spine treated by Albee's method of bone grafting; and the latter some cases of aneurism much improved by concussion of the seventh cervical spine. There are several other papers which it will repay the student to read attentively.

*The Principles and Practice of Obstetrics.* By JOSEPH B. DE LEE, A.M., M.D. Illustrated. \$8. (Philadelphia and London: W. B. Saunders Co., 1913.)

This ambitious text-book of more than a thousand pages is chiefly notable for the illustrations which, we are told, required "the tireless labor of three artists extending over a period of eight years." Most of the microscopic drawings by Miss Grace Amidon have been made from specimens; they are accurate and well done. Of the other illustrations a few are original, a few are taken from the author's text-book for nurses, but most of them have been redrawn from German works on obstetrics and embryology, especially from Bumm's *Grundriss zum Studium der Geburtshilfe*. Credit for these illustrations is not given at the place of insertion so frequently as is customary, though careful reading of the preface brings to light a frank acknowledgement of indebtedness. "To Bumm's matchless work," we read there, "the author is indebted for many ideas and for these, as well as for permission to copy some of his plates, the author is profoundly grateful." This statement, it seems to the reviewer, would be more accurate did it acknowledge indebtedness for some of the ideas and many of the plates.

Many of the ideas Dr. De Lee expresses are original. For example, in his introduction he declares that child-bearing is not a normal process. Such a gloomy view of reproduction would deserve severe criticism were not the book intended for physicians and medical students whose experience will demonstrate its incorrectness. Even in cases of contracted pelvis more than three-fourths of labors are normal. It is also novel to find in a text-book on obstetrics a discussion of the mental state of the unborn child—a discussion which leads to the conclusion that "a vague and obscure will intervenes in the production of these (fetal) movements." As a matter of fact, there is no evidence to indicate that the fetal brain functions; on the contrary we have reason to believe that the fetus is a spinal animal and that its movements are entirely reflex. An infant born without a brain may live several days, which proves that a brain is not needed

during fetal development. For similar reasons we cannot accept the view that the uterine contractions during labor cause the fetus pain.

We do not agree with the author in his opinion that he has been dogmatic in omitting polemics, but in another direction he has been very dogmatic. In the literature he selects for quotation he shows a strong bias. Thus, with regard to the problem of sex-determination, which has stimulated many biologists, to undertake investigations of fundamental importance, De Lee does not fairly summarize the facts as they are known to-day. So far as human beings are concerned the question remains unsettled, to be sure; but there is better reason to believe that sex is inherited from the spermatozoon than from the ovum. The opposite view is held by the author as he overlooks the observations of a number of investigators who found that in numerous animal species the spermatozoon is the vital factor in this problem. Similarly in describing fetal nutrition no reference is made to Cohnstein and Zuntz whose experiments have revealed in a very complete fashion the laws according to which gases pass through the placenta. This is all the more important since our knowledge of the mechanism by which other substances pass the placenta is very imperfect and in great part theoretical.

Although the author's views regarding the unsettled problems in obstetrics are not always in accord with the highest authority, his description of the more practical side of the subject is reliable and up to date. The book is logically arranged except for the section on the hygiene of pregnancy which should rightly precede the chapters on labor and the lying-in period. Two-thirds of the book are comprised in the sections on the pathology of pregnancy, labor, and the puerperium. Puerperal infection is discussed extensively and detailed directions are given for the performance of obstetrical operations.

*Nervous and Mental Monograph Series, No. 12. Cerebellar Functions.* By DR. ANDRÉ-THOMAS. \$3. (New York: The Journal of Nervous and Mental Disease Publishing Co., 1912.)

This is the most recent of the series of monographs published by the editors of *The Journal of Nervous and Mental Diseases*. The translation is good; and English readers, especially the otologists and neurologists, will find it highly entertaining and instructive reading. The author is an investigator of world-wide renown, and has made many contributions to the physiology of the cerebellar apparatus. It is to be regretted, however, that no mention is made of the clinical observations of Barony and the Vienna school.

The subject of cerebellar discords and their localization is but little understood at the present time, but great progress is now being made along this line. It is especially desirable, therefore, that those interested in neurology should acquaint themselves with this monograph, and, through its extensive bibliography, with the most important contributions to this subject.

S. J. CROWE.

*Progressive Medicine.* Edited by HOBART AMORY HARE, M.D., etc. Assisted by LEIGHTON F. APPLEMAN, M.D. Volume I, (Philadelphia and New York: Lea & Febiger, March, 1913.)

Any physician, who has not a knowledge of French or German, or the time to read widely, will keep himself well abreast of the times by the use of these quarterly volumes of *Progressive Medicine*. In this last one Frazier presents the newest information on the surgery of the head, neck, and thorax; Rührh on infectious diseases, including acute rheumatism, croupous pneumonia and influenza; Crandall on diseases of children; Wood on rhinology and laryngology, and Duel on otology. The articles are well prepared and interesting, and cover these different branches of medicine satisfactorily.

*American Association for Study and Prevention of Infant Mortality.* Transactions of the Third Annual Meeting, Cleveland, Ohio, 1912. (Baltimore: The Franklin Printing Co., 1913.)

The subjects especially discussed at this meeting were birth, registration, continuation schools, eugenics, progress in preventive work, mid-wifery, housing, and nursing and social work, all very important in the consideration of infant mortality. There are many interesting papers in this volume by Drs. Putnam, Holt, Helmholtz, Knox, Mr. Goddard, Miss Lathrop and others, and the transactions are a valuable source of information on a variety of topics relating to the welfare of infants. This new association is doing excellent work in a most fundamental line, and is becoming most helpful not only to physicians but to all social workers.

*A Practical Text-Book of the Diseases of Women.* By ARTHUR H. N. LEWERS, M.D. Seventh Edition. \$4. (New York: Paul B. Hoeber, 1912.)

This little volume belongs to an English Practical Series set, and possesses the general characteristics of this type of medical publication. It has long been well known and popular in the British Isles, and is evidently filling a place of usefulness, as is shown by the appearance of this seventh edition. The entire work has been revised and considerably enlarged, the chapters on cancer of the uterus and fibroid tumors particularly having been amplified in this revision. The orderly division of subject-matter, simplicity and conciseness of discussion, and the insertion of numerous illustrative cases adapt the book fairly well to the actual needs of the average medical student. It, however, must not be considered an exhaustive treatise on gynecology.

*Pathology and Treatment of Diseases of Women.* By A. MARTIN and PH. JUNG. English Translation of the Fourth German Edition. By HENRY SCHMITZ, M.D. \$5. (New York: Rebman Co., 1912.)

This English translation of one of the most authoritative, substantial and popular of the smaller German text-books on gynecology should be gratefully received by a large proportion of the American profession. The book is admirable in many respects. It is concise, judiciously comprehensive and logically arranged.

The numerous illustrations are helpful in elucidating the text, but are poor from an artistic standpoint. The translation has been clumsily done—that is, it is too literal, so that one encounters numerous sentences in which both the choice and arrangement of words are bad. These, however, are minor faults that do not seriously detract from the worth of the book. The pathological side of gynecology is brought strikingly into the foreground, a fact which, when one considers the eminence and experience of the authors, makes conspicuously evident one of the deficiencies of many of the American text-books on this subject. On the whole, the book will prove profitable reading alike to student and teacher, practitioner and specialist. It can be unhesitatingly recommended.

E. H. R.

*Diseases of Women.* By THOMAS GEORGE STEVENS, M.D., etc. (London: University of London Press, 1912.)

This little book can scarcely be considered as being more than a concise introduction to gynecology. As far as it goes, however, it is a creditable production, and is very readable. Certainly it will prove acceptable to those who desire only a superficial knowledge of this branch of medicine. The photomicrographs deserve special mention, inasmuch as they are far superior to those usually seen in manuals of this size. A perusal of the book leaves the impression that the author would be equal to a much more pretentious and valuable production.

*Private Duty Nursing.* By KATHARINE DE WITT, R. N. \$1.50. (Philadelphia and London: J. B. Lippincott Company, 1913.)

Miss De Witt has written a serviceable series of talks for nurses, which are now combined in neat book form. Many of them will be familiar to readers of the *American Journal of Nursing*. It is a rather sad commentary on the standards of nursing in this country that the authoress has to lay stress on points of etiquette. It would seem that common sense or the sense of propriety would prevent women making the mistakes they so often do. This is an excellent book for the ill-educated nurse, for Miss De Witt writes in a simple and effective way of what a private nurse should be, and of her responsibilities, and the advice given is helpful throughout. All the essential features of a nurse's relations with private patients are carefully considered, and she is shown clearly what she ought and ought not do.

## BOOKS RECEIVED.

*The Diseases of the Skin.* By Willmott Evans, M.D., B.S., B.Sc., F.R.C.S. With thirty-two illustrations. [1912]. 8vo. 375 pages. University of London Press, London; Oxford University Press, New York.

*The Medical Diseases of Children.* By T. R. C. Whipham, M.A., M.D. (Oxon.), M.R.C.P. With sixty-seven illustrations. [1912]. 8vo. 417 pages. University of London Press, London; Oxford University Press, New York.

*Minor Surgery.* By Leonard A. Bidwell, F.R.C.S. Second edition revised and enlarged. With one hundred and twenty-nine illustrations. [1912]. 8vo. 299 pages. University of London Press, London; Oxford University Press, New York.

*The Surgery of the Skull and Brain.* By L. Bathe Rawling, F.R.C.S. 1912. 8vo. 340 pages. Henry Frowde, London; Hodder & Stoughton, London.

*Health and Longevity Through Rational Diet.* Practical Hints in Regard to Food and the Usefulness or Harmful Effects of the Various Articles of Diet. By Dr. Arnold Lorand. 1912. 8vo. 416 pages. F. A. Davis Company, Philadelphia.

*The Labyrinth.* An Aid to the Study of Inflammations of the Internal Ear. By Alfred Braun, M.D., and Isidore Friesner, M.D. With fifty figures in the text and thirty-four half tones on thirty-two plates. [1913]. 8vo. 250 pages. Rebman Company, New York.

*Diet and Hygiene in Diseases of the Skin.* By L. Duncan Bulkley, A.M., M.D. 1913. 8vo. 194 pages. Paul B. Hoeber, New York.

*Report of the Pellagra Commission of the State of Illinois.* November, 1911. 1912. 8vo. 250 pages. Illinois State Journal Co., Springfield.

- Medical Men and the Law.* A Modern Treatise on the Legal Rights, Duties and Liabilities of Physicians and Surgeons. By Hugh Emmett Culbertson. 1913. 8vo. 325 pages. Lea & Febiger, Philadelphia and New York.
- The Principles and Practice of Obstetrics.* By Joseph B. De Lee, A. M., M. D. With 913 illustrations, 150 of them in colors. 1913. 4to. 1060 pages. W. B. Saunders Company, Philadelphia and London.
- Psychoanalysis.* Its Theories and Practical Application. By A. A. Brill, Ph. B., M. D. 1913. 8vo. 337 pages. W. B. Saunders Company, Philadelphia and London.
- The Development of the Human Body.* A Manual of Human Embryology. By J. Playfair McMurrich, A. M., Ph. D., LL. D. Fourth edition, revised and enlarged. With 285 illustrations, several of which are printed in colors. 1913. 12 mo. 495 pages. P. Blakiston's Son & Co., Philadelphia.
- The Surgical Clinics of John B. Murphy, M. D.* At Mercy Hospital, Chicago. December, 1912. Volume I. Number 6, 1912. 8vo. 931 pages. W. B. Saunders Company, Philadelphia and London.
- Guy's Hospital Reports.* Edited by F. J. Steward, M.S., and Herbert French, M.D. Vol. LXVI, being Vol. LI of the Third Series. 1912. 8vo. 412 pages. J. & A. Churchill, London.
- Golden Rules of Surgery.* By Augustus Charles Bernays, A. M., M. D., Hdibg., M. C. R. S., Eng. Second edition, revised and rewritten. By William Thomas Coughlin, M. D. 1913. 12mo. 281 pages. C. V. Mosby Company, St. Louis.
- Transactions of the American Gynecological Society.* Volume 37. For the year 1912. 1912. 8vo. 502 pages. Wm. J. Dornan, Philadelphia.
- A Reference Handbook of the Medical Sciences.* Embracing the Entire Range of Scientific and Practical Medicine and Allied Science. By various writers. First and second editions edited by Albert H. Buck, M. D. Third edition completely revised and rewritten. Edited by Thomas Lathrop Stedman, A. M., M. D. Complete in eight volumes. Volume I illustrated by numerous chromolithographs and 611 fine half-tone and wood engravings. 1913. 4to. 928 pages. William Wood and Company, New York.
- Transactions of the Royal Academy of Medicine in Ireland.* Volume XXX. Edited by J. Alfred Scott, M. A., M. D., F. R. C. S. I. 1912. 8vo. 521 pages. John Falconer, Dublin.
- Index-Catalogue of the Library of the Surgeon-General's Office, United States Army.* Authors and Subjects. Second series. Volume XVII, Suahel-Testut. 1912. 4to. 788 pages. Washington.
- Handbook of Diseases of the Rectum.* By Louis J. Hirschman, M. D. With one hundred and seventy-two illustrations, mostly original, including four colored plates. Second edition, revised and re-written. 1913. 8vo. 339 pages. C. V. Mosby Company, St. Louis.
- The Practice of Urology.* A Surgical Treatise on Genito-Urinary Diseases Including Syphilis. By Charles H. Chetwood, M. D., LL. D. Profusely illustrated. 1913. 8vo. 816 pages. William Wood & Company, New York.
- The Prospective Mother.* A Handbook for Women during Pregnancy. By J. Morris Slemons. 1912. 12mo. 343 pages. D. Appleton & Company, New York and London.
- Diseases of the Heart and Aorta.* By Arthur Douglass Hirschfelder, M. D. With an Introductory Note by Lewellys F. Barker, M. D., LL. D. 344 Illustrations by the Author. Second edition. 1913. 8vo. 738 pages. J. B. Lippincott Company, Philadelphia and London.
- The Illness and Death of Napoleon Bonaparte.* (A Medical Criticism.) By Arnold Chaplin, M. D. (Cantab.), F. R. C. P. With three illustrations. 1913. 12mo. 112 pages. Hirschfeld Brothers, London.
- Chloride of Lime in Sanitation.* By Albert H. Hooker. 1913. 8vo. John Wiley & Sons, New York; Chapman & Hall, London.
- Malaria. Cause and Control.* By William B. Herms, M. A. Illustrated. 1913. 8vo. 163 pages. The Macmillan Company, New York.
- The Surgical Clinics of John B. Murphy, M. D.* At Mercy Hospital, Chicago. February, 1913. Volume II, number 1. 8vo. 179 pages. W. B. Saunders Company, Philadelphia and London.
- Proceedings of the Canal Zone Medical Association.* Isthmian Canal Commission for the Half Year, April to September, 1911. Volume IV, Part I. [1911.] 8vo. 238 pages. I. C. C. Press, Quartermaster's Department, Mount Hope, Canal Zone.
- Glycosuria and Allied Conditions.* By P. J. Cammidge, M. D. (Lond.) 1913. 8vo. 467 pages. Longmans, Green & Co., New York; Edward Arnold, London.
- Dreams and Myths.* A Study in Race Psychology. By Dr. Karl Abraham. Translated by William A. White, M. D. Nervous and Mental Disease Monograph Series, No. 15. 1913. 8vo. 74 pages. The Journal of Nervous and Mental Disease Publishing Company, New York.
- Pathology.* A Manual for Teachers and Students. By W. T. Councilman, M. D. 1912. 8vo. 405 pages. W. M. Leonard, Boston.
- Mind and Health.* With an Examination of Some Systems of Divine Healing. By Edward E. Weaver, Ph. D. With an Introduction by G. Stanley Hall, Ph. D., LL. D. 1913. 12mo. 500 pages. The Macmillan Company, New York.
- The Johns Hopkins University Circular.* 1912. Volume XXXI. Whole Nos. 241-250. 1912. 8vo. The Johns Hopkins Press, Baltimore.
- Organic and Functional Nervous Diseases.* A Text-Book of Neurology. By M. Allen Starr, M. D., Ph. D., LL. D., Sc. D. Fourth edition, thoroughly revised. Illustrated with 323 engravings in the text and 30 plates in colors and monochrome. 1913. 8vo. 970 pages. Lea & Febiger, New York and Philadelphia.
- Progressive Medicine.* A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D. Assisted by Leighton F. Appleman, M. D. Volume I. March, 1913. 8vo. 361 pages. Lea & Febiger, Philadelphia and New York.



## PROSPECTUS OF SUMMER COURSES FOR GRADUATES IN MEDICINE.

## THE JOHNS HOPKINS UNIVERSITY—THE JOHNS HOPKINS HOSPITAL.

JUNE 2 TO JULY 15, 1913.

In cooperation with the Johns Hopkins Hospital, the following courses are offered to graduates in medicine. Instruction will begin on Monday, June 24 and end on Tuesday, July 15th.

The clinical courses are limited to graduates in medicine, but the courses in Physiology, Physiological Chemistry, Pharmacology and Therapeutics, and Bacteriology are also open to undergraduate students.

**PHYSIOLOGY.**

DR. C. D. SNYDER, Associate Professor of Physiology.

This course is intended to give the student an opportunity to become acquainted with some of the chief methods employed in teaching and in research.

Special attention will be given to the mechanisms of circulation and respiration that can be demonstrated upon mammals, and to methods of recording and accurately measuring such phenomena as venous pulse and venous and arterial pressures in man.

Monday, Wednesday and Friday, 8 a.m. to 12 m.

**PHYSIOLOGICAL CHEMISTRY.**

DR. E. K. MARSHALL, JR., Assistant in Physiological Chemistry.

This course will consist of lectures covering the chemistry of the proteins, sugars, fats, blood, muscle, urine, ferments, etc., and of laboratory exercises in which the various tissues and fluids of the body will be studied.

Tuesday, Thursday and Saturday, 2 to 5 p.m.

**PHARMACOLOGY AND THERAPEUTICS.**

DR. L. G. ROWNTREE, Associate in Experimental Therapeutics.

This course will consist of bedside instruction in therapeutics, and of laboratory demonstrations of the action of certain drugs, together with lectures on specific chemotherapy.

Monday, Wednesday and Friday, 2 to 5 p.m.

**BACTERIOLOGY.**

DR. L. P. SHIPPEN, Instructor in Hygiene and Bacteriology.

This course will consist of practical laboratory exercises covering the preparation of culture media, the principles of sterilization and the methods of isolating, cultivating, and studying bacteria.

Tuesday, Thursday and Saturday, 10 a.m. to 1 p.m.

**MEDICINE.**

The following courses will be given:

I. **Practical Medicine**—DR. L. V. HAMMAN, and DR. F. J. SLADEN, Associates in Medicine.

A course in practical medicine consisting of ward rounds. Daily, 9 to 11 a.m.

II. **Clinical Microscopy**—DR. C. G. GUTHRIE, Instructor in Charge of the Clinical Laboratory.

The course consists of lectures and laboratory work, the material from the wards being utilized.

Monday, Wednesday and Friday, 2 to 4.30 p.m.

III. **Serum Diagnosis**—DR. P. W. CLOUGH, Instructor in Charge of the Biological Laboratory of the Medical Clinic and DR. C. R. AUSTRIAN, Assistant in Charge of the Laboratory of the Phipps Dispensary.

The course consists of lectures and laboratory instruction covering the Wassermann reaction, Widal reaction, etc.

Tuesday, Thursday and Saturday, 2 to 4.30 p.m.

IV. **Diseases of the Circulation**—DR. A. D. HIRSCHFELDER, Associate in Charge of the Physiological Laboratory of the Medical Clinic, and DR. G. S. BOND, Assistant in Medicine.

The course covers the diagnosis and treatment of cardiac diseases, together with a study of blood-pressure, venous pulse, electrocardiograms, etc.

Tuesday, Thursday and Saturday, 2 to 4 p.m.

V. **Percussion and Auscultation**—DR. L. H. HAMFLETT, Associate in Medicine, and DR. S. WOLMAN, Instructor in Medicine.

Tuesday, Thursday and Saturday, 11 a.m. to 1 p.m.

VI. **Diseases of the Digestive Apparatus**—DR. T. R. BROWN, Associate in Medicine.

A course in the diseases of the digestive apparatus, with practical exercises in the use of the various diagnostic methods including sigmoidoscopy and fluoroscopy.

Monday, Wednesday and Friday, 11 a.m. to 12 m.

**SURGERY.**

The following courses will be given:

I. **Surgical Diagnosis**—DR. J. M. T. FINNEY, Professor of Clinical Surgery, assisted by DR. J. C. BLOOMER, Associate Professor of Surgery, DR. R. H. FOLLIS, Associate in Surgery, and DR. G. J. HEUER, Instructor in Surgery.

This course will consist of daily ward rounds and operating clinics.

Rounds: 9 a.m. to 10 a.m., and operations, 11 a.m. to 12 m.

II. **Surgical Pathology**—DR. W. E. DANDY, Assistant Resident Surgeon. This course will consist of the gross and microscopic study of specimens from the surgical operating room.

Tuesday, Thursday and Saturday, 2 to 5 p.m.

III. **Operative Surgery on Animals**—DR. GEORGE WALKER, Associate in Surgery, assisted by DR. W. A. FISHER, Instructor in Surgery, and DR. R. D. McCLEND, Assistant in Surgery.

In this course a limited number of students will perform a series of operations in abdominal, renal and blood-vessel surgery, under the immediate supervision of the instructors.

Monday, Wednesday and Friday, 2 to 5 p.m.

IV. **Genito-Urinary Surgery**—DR. J. T. GERAGHTY, Associate in Genito-Urinary Surgery, and DR. A. KIDNELL, Assistant Surgeon.

(a) Clinical instruction in history taking, routine genito-urinary examinations, urinary analysis, methods of microscopic examinations of secretions from the urethra, venereal sores (treponema pallidum), prostatic, etc., instrumental examination (including urethroscopy, but not cystoscopy), and methods of treatment.

Daily, 10 a.m. to 12 m.

(b) A course in cystoscopy and the diagnosis of renal conditions will be offered by Dr. Geraghty to a limited number of students who have had previous training in urology. This will consist of instruction in the methods and technique of cystoscopy, ureteral catheterization, and renal functional and differential diagnosis.

Tuesday, Thursday and Saturday, 12 to 1.30 p.m.

V. **Orthopedic Surgery**—DR. R. FAYEWEATHER, Assistant in Orthopedic Surgery.

Instruction in the methods of diagnosis and treatment, with particular attention to bone and joint tuberculosis and the various non-tuberculous joint affections.

Monday, Wednesday and Saturday, 10 to 12 m.

Instruction in the treatment of scoliosis will be given. Rounds will be made in the public wards one morning of each week.

Thursdays, 10 to 12 m.

VI. **Plastic Surgery**—DR. J. S. DAVIS, Instructor in Surgery.

In this course particular attention will be paid to wound healing, skin grafting, etc. Ward, dispensary and operative demonstrations will be given.

Monday, Wednesday and Friday, 10 to 12 m.

VII. **Rectal Surgery**—DR. H. B. STONE, Assistant Surgeon.

This course will include digital and proctoscopic examinations, together with operations under general or local anesthesia.

Tuesday, Thursday and Saturday, 10 to 12 m.

VIII. **Radiography**—DR. F. H. BAETJER, Associate in Actinography, assisted by DR. C. A. WATERS.

Practical instruction in X-Ray laboratory. Daily, 10 to 12 m. Lecture on Saturday at noon.

IX. **Anesthesia**—DR. J. P. PRATT, Assistant Resident Surgeon.

Practical instruction in the administration of anesthetics in the operating room.

Tuesday, Thursday and Saturday, 10 to 12 m.

**GYNECOLOGY.**

The following courses will be given:

DRS. G. L. HENNER, C. F. BURNAN and E. H. RICHARDSON, Associates in Gynecology, and DR. C. W. VEST, Resident Gynecologist.

I. **Operative Clinics**, preceded by pelvic examinations under anesthesia.

Daily, except Friday, 9 a.m. to 12 m.

II. **Ward-rounds**—Tuesdays and Thursdays, 9 to 10 a.m.

III. **Practical Work in the Dispensary**, including history taking, pelvic and abdominal examinations without anesthesia, and medical gynecology. Daily, 2 to 4 p.m.

IV. **Gynecological Pathology**—DR. ELIZABETH HURDON, Associate in Gynecology.

Gross and microscopic demonstration of specimens, and a special course in the examination of material removed by curettage.

Monday, Wednesday and Friday, 12 to 1 p.m.

V. **Cystoscopy**—DR. G. L. HUNNER.

Practical demonstrations in the cystoscopic clinic. Tuesday, Thursday and Saturday, 2 to 4.30 p.m.

**PEDIATRICS.**

DR. JOHN HOWLAND, Professor of Pediatrics, and DR. E. A. PARK, Instructor in Pediatrics.

The course will consist of clinics and demonstrations of patients illustrating the more common diseases of infancy and childhood, especial emphasis being laid upon the methods of treatment of the nutritional diseases of infancy.

Monday, Wednesday and Friday, 11 a.m. to 1 p.m.

**FEES.**

A full day's work for the entire period in as many courses as can be taken without conflict in hours—\$100. If Animal Surgery is taken, an additional charge of \$25.00 will be made.

The fee for any one of the following courses is \$25.00:

Physiology,	Orthopedic Surgery,
Physiological Chemistry,	Plastic Surgery,
Therapeutics,	Rectal Surgery,
Bacteriology,	Anesthesia,
Clinical Microscopy,	Gynecological Pathology,
Serum Diagnosis,	Gynecological Cystoscopy,
Diseases of Circulation,	Gynecological Dispensary,
Digestive Diseases,	Pediatrics.

The fee for any one of the following courses is \$50.00:

Medical Ward Rounds,	Surgical Diagnosis with Ward
Radiography,	Rounds,
Gynecological Operative Course	Genito-Urinary Surgery (a).
with Ward Rounds,	Genito-Urinary Surgery (b).
Surgical Operations,	

For Animal Surgery alone the fee is \$75.00.

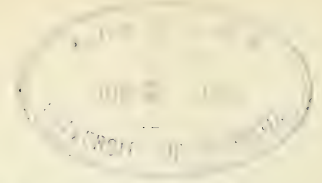
Persons desiring to take any of these courses must register at the Dean's Office, where they will receive the necessary credentials.

Courses cannot be changed after registration, except upon the payment of an additional fee.

In view of the fact that only a limited number can be admitted to some of the courses, it is advisable that applications be made in advance. Address the Dean of the Johns Hopkins Medical School, Baltimore.

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June



# BULLETIN

OF

# THE JOHNS HOPKINS HOSPITAL

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## SPECIALISM IN THE GENERAL HOSPITAL.\*

By SIR WILLIAM OSLER, BART..

*Regius Professor of Medicine, Oxford; Honorary Professor of Medicine, The Johns Hopkins University.*

It is not easy to put in words my appreciation of the honor of delivering one of the formal addresses at the opening of this institute or to express my gratification at the inauguration of this new development in the Johns Hopkins Medical School. The pleasure is heightened by the thought that the generosity of an old and valued friend has made today possible. This hospital has already experienced the wise liberality of Mr. Henry Phipps, one of whose tuberculosis foundations, under its management, ranks as a model of its kind.

That, after nearly a quarter of a century, all those professionally concerned in the early working of the hospital are here to take part in this ceremony, is, for us at least, a happy circumstance. One man I should like to have seen with us, Francis T. King, the first president of the hospital, whose devotion to its interest and whose faith in its future were the stay and support of his declining years. Three of those closely connected with the early organization have passed away. Dr. John S. Billings was, from the first, the adviser of the board of trustees, the real designer of the hospital, and the friend to whom we all turned for advice. I know with what satisfaction he looked back on this part of a life great in achievements for the public and the profession.

\* Remarks made at the opening of the Henry Phipps Psychiatric Clinic of The Johns Hopkins Hospital, April 16, 1913.

No one of all that fine band of men with whom we were associated, Judge Dobbin, Judge Gwinn, Mr. Francis White, Mr. Lewis Hopkins, Mr. W. T. Dixon, Mr. G. W. Corner, Dr. Cary Thomas, Dr. Alan Smith, Judge Brown, Mr. James Cary, Mr. Joseph Elliott, Mr. C. Morton Stewart, would have appreciated to-day more keenly than Daniel C. Gilman, whose work in connection with the opening of the hospital must never be forgotten. He was a man with rare vision and one also who could drive the straight furrow, as the people of this state—of the country at large—well know. And how Isabel Hampton would have rejoiced to see this day—with its great opportunity to develop the special work so dear to her heart. How full of gratitude must be our first director, Dr. Hurd, to see the fruition of many years of strenuous, hopeful toil!

In 1889 this institution seemed to many the last word in hospital construction, and those of us who were fortunate enough to take charge of the departments felt that here was something to be lived up to, something in which our dreams could be realized. Only when in working order did we feel its incompleteness. We had no medical school, a big gap quickly filled by the generosity of Miss Garrett and her friends. Year by year saw new departments added, new lecture rooms, operating rooms, laboratories, additions to the out-patient de-

patients, to the Nurses' Home, and, by Mr. Mariou, to the private wards; and hand in hand, an internal growth in efficiency, and an ever-widening sphere of influence, educational and philanthropic. Our ambition was to do for medicine what Mr. Gilman and his faculties of the university were doing in arts and science, and at a pace hard to follow. The race was not an easy one, but fortunately there were close bonds between the two training stables, and we had the advantage of the prestige of their 13 years of brilliant success.

Only a few impressions of life endure. We use the same cylinders over and over again, the dots and markings become confused, and when we call for a record, a jumbled medley is poured out, a confused message from the past. But certain records are time-fast, and bite in such a way that no subsequent impressions can blur the clearness, and the story comes out fresh and sharp. So it is when I call up those early years so full of happiness, so full of hope. And to have seen in so many ways the fulfillment of our heart's desire is more than we could have expected, more indeed than we deserved.

I am sorry for you young men of this generation. You will do great things, you will have great victories, and, standing on your shoulders you will see far, but you can never have our sensations. To have lived through a revolution, to have seen a new birth of science, a new dispensation of health, reorganized medical schools, remodeled hospitals, a new outlook for humanity, is not given to every generation.

By temperament a dreamer, wherever I have worked, visions of the future have beset me, sometimes to my comfort, more often to my despair. In desolate days I have wandered with Don Quixote, tilting at windmills; in happier ones I have had the rare good fortune to dream dreams through the gate of horn, and to see their realization, to have both the vision from Pisgah and the crossing of Jordan. I have seen the school at which I began in Toronto, in an old building, dirty beyond belief, transformed into one of the most flourishing on the continent, a staff of seven teachers increased sevenfold; my alma mater, McGill, prosperous even then in men of mettle, but housed in wretched quarters, now in palatial buildings, and in affiliation with two of the best equipped of modern hospitals. How paltry were my aspirations of those days! How insignificant do they seem. My feelings when Sir Donald Smith, now Lord Strathcona, gave us the first endowment of \$50,000, could not be stirred to the same intensity to-day by less than a million! Nearly 30 years have passed since I joined the University of Pennsylvania, the premier school of the country. There were new buildings, and a new hospital grouped about a single arts building. But what a transformation since! Whole squares of West Philadelphia annexed and covered with laboratories, dormitories and lecture halls and largely due to the magic energy of a prince of dreamers, William Pepper.

It has been my lot to see others do what I should have liked to do myself, and to feel that it has been better done! Looking back over a somewhat vagrant career, my fission from an academic body has always been a stimulus, and has invariably quickened the pace of progress. And this thought was a con-

solation when I left this comfortable billet, a few years ago. Among the scanty seeds scattered in my peaceful valedictory only those in which I ventured into the dangerous region of prophecy appear to have fallen on good ground.

I spoke of the needs of special departments—hoping that within 25 years we should have a psychiatric institute, a children's hospital, a genito-urinary clinic and a special building for diseases of the eye, ear and throat. Two of these are already accomplished facts—the Harriet Lane Johnston Children's Department, has been opened; to-day we open the Phipps Psychiatric Institute, and for the new genito-urinary clinic, that money has been furnished through the liberality of Mr. James Buchanan Brady. Others will follow rapidly, and it is safe to say that within a dozen years there will be as many special departments, semi-independent units in a great organization. The occasion seems fitted for the expression of a few thoughts on specialism in the general hospital.

The work of the units is identical; each a place where rich and poor receive the best skilled help that the profession can command; each a place where students are taught; each a center of study and research. Let us consider briefly these three functions. Similar in diversity, each unit in organization, in aims, and in methods, is a replica of the other. Each represents a technical school linked to the university by the medical faculty of which, by Mr. Hopkins' will, this hospital was to form a part. They differ from the more purely scientific departments of the medical school in one important particular. The hospital units mint, for current use in the community, the gold wrought by the miners of science. This is their first function.

A mother to-day brings her child to Dr. Harry Thomas, at the neurological department, a poor dwarfed, idiotic creature, but all the same very dear to her heart. It is a far cry from the little laboratory where Schiff made his immortal experiments, and literally thousands of workers in the mines of science have slaved years to find the pure gold, handed out freely from this hospital to that poor woman, with which salvation was wrought for her poor child. It seems so easy now. "Ah, a cretin. How interesting! How old do you say? Eight? Why, she looks three. All right, do not worry, the child will get well quick; get these powders. Yes, three times a day!"

An anxious mother, whose son goes to Manila next week, brings him to Dr. Barker in the private ward for an anti-typhoid inoculation. Again a far cry from Zurich, where Klebs—so often a pioneer—first saw the typhoid bacillus. Again, a host of miners and a vast store of gold—golden knowledge, with which, would they but use it, people of the country could redeem from certain death thousands of their sons and daughters.

The two incidents I have mentioned illustrate what is going on in every unit of a hospital today. Take another—that street brawl last night. "Yes, he was shot through the abdomen." "A dozen wounds in the bowels, you say? Hum! What a job! Must have taken you a long time—doing well,



of course." "Oh, yes, we got him early—they all do well now!" Who would have believed such a story in my student days? Again, the pure gold dug out by the elder Gross, Lister, Halsted and thousands of miners, minted in the laboratories and handed out, Mr. President, to the public last night by your surgeons.

We sit over the fire in the evening and pile on the coal without a thought of the dark and dangerous lives of the poor miners who risk so much for so little. It distresses my soul to think that we have done so little for the miners of science, and it does not lessen my distress to know that very often they do not give a thought to us. That coal put on the grate last evening—do you think the Hungarian in West Virginia thought how comfortable you would be over the fire? No! Nor did Schiff realize that his work would be utilized to brighten the hopes of thousands of mothers or that he was following a lode richer for humanity than the Golden Fleece. Only a cold-hearted, apathetic, phlegmatic, batrachian, white-livered generation, with blood congealed in the cold storage of commercialism, could not recognize the enormous debt which we owe to these self-sacrificing miners of science; and yet there are to-day sons of Belial, brothers of Schimei, daughters of Jezebel, direct descendants of the Scribes, Pharisees and hypocrites in the time of Christ, who malign these prophets and wise men, winners in a fight for humanity unparalleled in the annals of the race.

The perfect physical form in man or woman is much more sought than found. The perfect mental form is even more rare. The best to hope for in the average man, from nature and nurture, is to have a right judgment in all things. In how few of us is this consummation reached! One philosopher made the comforting remark that "Every man has a sane spot somewhere." Burton, in his survey of humanity in the famous *Anatomy of Melancholy* concludes that the whole world is mad, and needs a journey to Anticyra, (where the best hellebore, a specific against madness, was grown).

There should be, Mr. President, no lack of candidates for help from the unit we open to-day. Many a man goes to his physician now for an overhauling of his machinery. I found a big West Virginian in the private ward one morning. The history was colorless. I went over him thoroughly. "There is nothing the matter with you," I said. "I did not say there was," came the reply, "that is what I wanted to know."

We are all a bit sensitive on the subject of our mental health, but a yearly stocktaking of psychic and moral states, under the skilled supervision of Professor Meyer, would be most helpful to most of us.

Mr. J. A tendency to irritability of temper.

Mrs. R. Too much given to introspection.

Miss B. Over-anxious about her soul.

Master G. Worried by a neurasthenic mother.

These would be some of the headings in the diagnosis slips. But the Institute will have enough to do—meeting a demand for the early treatment of borderland and acute cases.

The progress in the rational treatment of insanity is a

bright chapter in the history of the past century. The story recently told by Dr. Hurd, of the changes in this country within forty years, is full of encouragement. The larger staff, the skilled assistants, the scientific study of the cases has become a rule and this community has had the benefit of the up-to-date methods of the Sheppard-Pratt Hospital, and has seen with pride the rapid development of the work of the state institutions. New methods of treatment will be tested, every advance in technique controlled, and to new theories will be applied the touchstone of science. A wide diffusion of its benefits should take place through the nurses who will pass through the institute. The discreet, even-balanced, thoroughly trained mental nurse will be a great boon in general practice, and she will have a sociological value amid the widespread activities that have been aroused in connection with mental hygiene.

That the medical student is an essential factor in the life of a great general hospital, has been of slow recognition in this country. Admitted to the dispensaries, welcomed in the amphitheater, he has been, until recently, rigidly excluded from the wards, except as a casual attendant on ward classes. I am glad to say that from the day he leaves the medical school laboratories, he is in this hospital a co-worker with doctors and nurses, in every one of its activities, and as his right, not as a privilege grudgingly granted by the trustees.

And so it should be in all general hospitals. Every unit must be so organized as to make him fit in as part of its machinery. It is his business to know disease, and for the sake of the public, every possible opportunity should be given to him. I would even throw open the private wards, that the clinical clerks and surgical dressers might see the vagaries of sick life in all classes of society. In the palmy days of Rome, the physician was followed to the houses of the wealthy by his pupils—a practice we could emulate in our private wards—limiting, of course, the numbers, and selecting the cases.

But with the medical student there is a real difficulty, expressed 25 centuries ago by the Father of Medicine, in the famous aphorism "Life is short; the art is long". The stay of the medical student in the hospital is so brief, the amount to be learned so vast, that we can only hope to give him two things—method (technique) and such elementary knowledge as how to examine patients, the life history of a few great diseases and the great principles of surgical practice. He cannot be expected in the short period of the curriculum to go the circle of the units, spending time enough in each to master the chief details of a dozen specialties.

In most schools, a system of elective studies has been arranged to meet this really pressing and serious condition, which has grown in acuteness with the multiplication of the specialties? How can an institute like this touch the medical curriculum? At many points, directly and indirectly. The very existence in a general hospital indicates the recognition of psychiatry as part of its legitimate work. One of the tragedies of the subject has been a dissociation from centers of active professional and university life. A department of medi-

cine, with the closest affiliation with the life of the community, has been segregated and stamped with a taboo of a peculiarly offensive character. Here it will take its proper place—a unit in the work of the medical school of a university.

This, in itself, will be a lesson to the student. A new atmosphere will be diffused, a new group of energies and activities will come into the hospital, which cannot but be helpful. The director, his staff, and the nurses will play a new rôle, which will greatly enhance the reputation of the old company. Living as he does in such close fellowship with the staff of the hospital, the medical student will be influenced in this way by the very presence of the institute.

It is to be hoped too, time may be found for general instruction of the senior class in the elements of neuro-psychology, and with the elective system, an active group of students be found to whom this study will appeal strongly. But after all as practical men, we have to face the Hippocratic aphorism—the art is getting longer and longer, the brain of the medical student, not getting bigger and bigger, has its limits; and though keener and more industrious than ever in history, the time is too short for a man already burdened to the breaking point, to study any specialty from the standpoint of the specialist.

To a large outside body, this institute should cater with extraordinary benefit. There must be a thousand or more assistants in the asylums of the country, whose pineal glands are not yet crystallized, and who should find here inspiration and help. Amid isolated and depressing surroundings, these men do yeoman work in the profession. From the director and his staff, they will receive that warm and encouraging sympathy, the very leaven of life, a quality which has been the inspiration of the benefactions of the founder of this institute. And I hope room and plenty of it will be found for the general practitioner, through whom more than any other group, the benefits of this institute may be distributed. He needs enlightenment, instruction and encouragement—enlightenment as to the vast importance of early deviations from normal mental states, instruction in new methods of diagnosis, and treatment and encouragement to feel that in the great fight for sanity in the community he is the man behind the guns.

A larger outlook is connected with the third function of a hospital unit. The old Greek, with his quick sense of helpfulness, always asked about a work: "Does it make life a better thing?" and Prof. Gilbert Murray remarks that one who wished to give the greatest praise to the Athenians said, "They strove to make gentle the life of the world." The American, the modern Greek—mentally if not orally—always asks the same practical question; sometimes, in the case of pure science, when it is both foolish and fruitless. But he may ask legitimately how such an institute as this may be helpful in studying lapses and freaks of the human mind—I cannot give the answer. "It is not in the book I learned out of" as the children say. I could tell you in internal medicine, and could refer you to the long list of studies in dysentery,

malaria, typhoid fever, pneumonia, heart diseases and blood diseases that have come from the medical unit. But a psychopathic unit is a novelty in a general hospital, designed for the study as well as for the cure of mental aberrations.

We talk a great deal about the human mind, and, when cornered, quote Hamlet to cover an unpleasant ignorance of its true nature. The modern student, like the ancient, takes his stand either with Plato and compares the mind and brain to a player with his musical instrument, or with Lucretius to a musical box wound up for so many years to play so many tunes. Authorities lean to one or other of these views, and I have a shrewd suspicion that some of our distinguished visitors, great representatives in this specialty, do not see eye to eye in this matter. Three things we do know, departures from normal states are extraordinarily common—they are the most distressing of all human ills—they should be studied systematically by experts, with a view to their prevention and cure.

When Dean Swift left the little wealth he had to found a house for fools and mad, he could not forego the pleasure of adding the satiric touch: "No nation needed it so much." This idea, was not, I am sure, in the large heart of Mr. Phipps; but a wide-spread feeling has arisen in this country that the hygiene of the mind is just as important as the hygiene of the body—that we must return to the Greek ideal of the fair mind in the fair body. How beautifully Plato visualizes the day (in a passage I am never tired of quoting)—"When our youth will dwell in a land of health amid fair sights and sounds and receive good in everything; and beauty, the effluence of fair works, shall flow into the eye and ear like a health-giving breeze from a purer region, and insensibly draw the soul from earliest years into likeness and sympathy with the beauty of reason." (Republic, Bk. II.)

What a revelation of an awakening in the community that it was possible to organize such a Congress of Mental Hygiene as was held here a few months ago under the auspices of the Medical-Chirurgical Faculty! The program itself was an inspiration. In this country, to recognize a wide-spread need is to meet it; and such gatherings held under auspices of the National Committee will go far to lessen the sad prevalence of early nervous breakdown.

What a philosopher said of the Melissians may be said of many people—they are not fools, but they do just the things that fools do, in the matter of training the young. Unfortunately, we cannot pick our parents, and still, as of old, our hearts give our hands, regardless of our heads. Dr. Mott will tell a tragic tale of heredity in relation to insanity. I am afraid several generations must pass before we see any practical results of the present active eugenic crusade, but there is an immense and hopeful work to be done in educating parents in training-stable methods. An Ethiopian cannot change his skin, but a queen bee results from a change of diet. This institute, I am sure, will play its part in this national campaign of prevention of mental ill health through education—a campaign as important to the public, and just as

worthy of support as the great struggles against tuberculosis and infant mortality.

It will be helpful too, to study in a sane, sober and sympathetic way, epidemics of mental, moral and even economic folly as they sweep over the country. The present opportunity should not be missed. With causes just as definite as small-pox or yellow-fever, they never occur under exactly the same conditions, but all have their basis in, and are mere specks upon, that fine old humanity that is ever fighting its way towards the light.

The present out-break has not been equaled since the capture of the Roman world by Oriental cults. The same old-fashioned credulity exists that enabled Mithras and Isis, Apolonius and Alexander to flourish then as the new cults do to-day—and for the same good reason. There is still potency in the protoplasm out of which arose in primitive man, magic, religion and medicine. Circe and Ascalapius were probably twins! Historically our fringe of civilization is of yesterday, if we compare the six or seven thousand years of its record with the millions which must have passed since man assumed his present form on the earth. In this vast perspective Aristotle and Darwin are fellow-students; Hippocrates and Virchow are contemporaries.

Primitive views still prevail everywhere of man's relation to the world and to the uncharted region about him. So recent

is the control of the forces of nature that even in the most civilized countries man has not yet adjusted himself to the new conditions, and stands, only half awake, rubbing his eyes, outside of Eden. Still in the thaumaturgic state of mental development, ninety-nine per cent of our fellow creatures, when in trouble, sorrow or sickness, trust to charms, incantations and to the saints. Many a shrine has more followers than Pasteur; many a saint more believers than Lister. Less than 20 years have passed since the last witch was burned in the British Isles!

Mentally the race is still in leading strings, and it has only been in the last brief epoch of its history that Esop and Lewis Carroll have spun yarns for its delight, and Lucian and Voltaire have chastized its follies. In the childhood of the world we cannot expect people yet to put away childish things. These, Mr. President, are some of the hopes which fill our hearts as we think of the future of this new department.

One word of appeal to the units. Members of a corporate body, successful life will depend upon the permeation by harmonics which correlate and control the functions. Isolation means organic inadequacy—each must work in sympathy and in union with the other and all for the benefit of the community—all toward what Bacon calls the lawful goal of the sciences, that human life be endowed with new discoveries and power.

## SOME MODERN PROBLEMS IN NUTRITION.\*

By DR. FRANZ KNOOP,

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Physiological chemistry is concerned with the chemical rearrangements which are constantly in progress in all living organisms. The continuity of these transformations is probably the most striking characteristic of what we term "life."

Physiological chemistry finds its greatest support from the uses which practical medicine makes of its results, and thus to a large extent it has dedicated itself to the task of elucidating all the chemical changes occurring in the human organism. The most direct way to attack this extraordinarily complicated problem as a whole, is to make a comparison of the chemical composition of the organism's intake and output. Physiology has devoted itself, at enormous expense, to investigations aiming at the attainment of an exact metabolic balance. This method of investigation furnished chiefly quantitative results, for qualitatively, it concerned itself with substances which, from a chemical point of view, were exceedingly ill-defined. By degrees, this drawback has been in part removed. For example, the main facts, concerning the chemistry of the proteins have only been recognized during the present century.

Cellular material from plants and animals, especially mam-

mals, constitutes the main source of our food substances. Hence the study of these food substances is closely allied to the chemical analysis of the human body, for the latter, considered from the standpoint of chemical classification, does not differ essentially from the animal food which supports it.

These descriptive studies, which we may regard as a sort of chemical anatomy of the human body, are essential for the intelligent investigation of the chemical functions of the body. They are the more important, since the food substances of the body are not utilized as is the fuel of an engine, whose parts are independent of its source of energy. In the animal organism, the food units have actually to furnish the ever-changing parts of the machine consuming them. The constant regeneration of these parts constitutes an important part of their chemical functions.

Anatomy and physiology are seldom so intimately united, as when function and composition of cell aggregates are considered from a chemical standpoint. It is surely a sign of a lack of understanding when descriptive chemical studies of this character are regarded by physicians as purely chemical, simply because their biological significance is not obvious at the present time. It is true that pure chemists, without any biological interests, may take up work of this character and, indeed, they have done so in many lines of investigation. But

\* Paper read at a meeting of The Johns Hopkins Hospital Medical Society, March 17, 1913.



often this has not been done, and then it is left for biology to fill the ground, which may yield a harvest to succeeding generations only.

Metabolic physiology, using the term in the old sense, knew but little of the detailed structure of the food substances. It concerned itself with the needs of the entire organism under the most varying conditions, with the availability, thermodynamic effect, value and utilization of the individual food-substances for various purposes. The experimental conditions were varied to include work and rest, hunger and satiety, foetal life, youth and old age, fever, subnormal temperatures and hibernation, the effects of high altitudes and sea-level, and so on. Valuable information was gathered in this way, but progress beyond a certain point was impossible, and from a purely chemical point of view, such studies were not particularly fruitful, for nothing definite was known as to what substances were qualitatively essential to the organism. Thus, meat which has been extracted with ether is lacking in a certain substance which cannot be replaced by the definitely characterized chemical substances of the ether-extract, and the experimental animal, fed with such extracted material, ceases to thrive. Feeding exclusively with polished rice leads to a fatal condition with the development of symptoms similar to beri-beri. These symptoms may be quickly and completely abolished by the administration of about one milligram of a substance contained in that part of the rice which has been discarded. This substance belongs to none of the known groups of food-substances. What is it? Is it always necessary, or only in conjunction with a rice diet? We do not know. In questions of this nature, we feel our ignorance on every hand.

The methods of metabolic physiology in which only the gross effect is considered, can help us but little in obtaining an insight into these chemical changes, the elucidation of which promises an altogether deeper insight into the varied types of vital processes. The recent development of biochemistry has clearly shown, that we stand only at the threshold of such new points of view. Historically, how much better off morphology appeared, which, having at its disposal highly developed optical methods of investigation, gave such an overwhelming stimulus to the tendency to consider all the problems of natural science from a descriptive point of view, that, for a time, it was believed that the most important problems of function could be solved by the microscope. Even now, in the education of medical students, we find descriptive methods still predominating to an extent, which is only historically intelligible. Necessary as a knowledge of cellular structure is for the understanding of function, we must remember that, to quote the words of Hofmeister, the microscope shows us only the empty stage, the action on which is revealed to us only by totally different methods of research.

What is true for the individual cell is equally true for the whole body with its various organs. We are more and more struck by the fact that relations between different parts of the body are not exclusively controlled by visible morphological factors, and I need only mention the names adrenalin,

and secretin, pituitrin and iodothyrene, to recall to your mind a series of organs about whose chemical functions we are partially informed, but about which anatomical investigation has taught us almost nothing. Starling introduced the conception of hormones for these carriers of chemical impulses, among which may be mentioned the body causing the proliferation of mammary tissue following the injection of foetal extracts. Here, where the work of Jacques Loeb on the chemical stimulation of development is so well known, it is unnecessary to emphasize the prime importance of chemical studies with regard to processes which, in the past, have been relegated exclusively to morphological investigation.

The hormones which regulate the vital activities of the whole body, are produced by the organism itself, and the chemistry of the formation of these substances must be altogether distinct from the normal breakdown of food material. We can hardly hope to understand these special reactions until we have attained an adequate picture of the normal catabolism of the substances which primarily furnish energy to the organism. Metabolic physiology has had little to say concerning these matters. It has indicated the possibility of the mutual replacement and possible interconversion of some of the main groups of food-substances, and it has shown that the conversion of protein, fat and carbohydrate to carbon dioxide, water, urea and sulphuric acid does not always follow the most direct path. But knowledge as to how these reactions occur and how they may be modified, can only be obtained from a detailed chemical analysis of these intricate changes, and at present our methods are inadequate for the task. If we consider as our first and final quest the formulation of equations which shall indicate, step by step, the gradual conversion of food-substances into the end products of metabolism, we shall find much that is helpful and stimulating. Oxidation reactions in the living organism are characterized by their slowness and regularity and the constancy of such conditions as temperature, pressure, reaction, etc., constituting a mechanism that we can hardly hope to imitate. It is the unique and extraordinarily complete character of this mechanism of the living organism, that makes it so generally interesting a subject for investigation.

After metabolic physiology had been for some time in a state of stagnation, the new ideas leading from a chemical conception of the intermediate paths of catabolism, quickened the whole subject into renewed activity. Unsuccessful attempts had long been made to try to determine in the normal organism intermediate products, which would directly indicate the paths of normal metabolism. This is a most remarkable fact. We may perhaps understand this best if we assume that only a few molecules of a substance undergo oxidation simultaneously, and that their catabolism is complete before new molecules are attacked. Thus but few molecules will, at any one time, be in the first, second or third stages of oxidation, and the concentration of intermediate products of catabolism must always be low.

It was only when pathological or experimentally changed conditions were made use of, or isolated surviving organs were

employed, or the fate of foreign substances in the body was investigated that certain laws were developed, which subsequently proved to be applicable to the normal organism. Up to this time practically only hydrolytic changes, such as the breaking up of CO and CN groups with addition of water, had been observed. This type of change is seen in the conversion of protein into amino-acids with intermediate formation of albumoses and peptones, or in sugar production from starch, or fatty acids and glycerine from fats. But none of these reactions, which are effected by the digestive ferments, involve oxidation and they liberate no significant amount of energy and bring about no alteration in the chains of carbon atoms. The type of change involved in oxidation was first recognized in connection with the fatty acids, but even here, in spite of the fact that about 100 grams a day may be burned, it was impossible to isolate intermediate products directly. When, however, a group resistant to attack in the body was introduced into the fatty acid molecule, it became possible to detect intermediate products. For this purpose phenyl substituted fatty acids were employed, the homologues of which are found among the products of intestinal putrefaction and which are constantly being absorbed. By using these substances, it was possible to show that fatty acids undergo oxidation in such a way that the oxygen invariably attaches itself to the  $\beta$ -carbon atom and the ketonic acid thus formed yields, on further oxidation, a saturated fatty acid, containing two less carbon atoms.

Thus it has been possible to determine the chief path followed by the fatty acids in their breakdown and to recognize the intermediate products which we are likely to encounter. This conception has led to an intelligible understanding of the origin of the acetone bodies from fatty acids in the diabetic organism. Similarly, the fact that the fatty acids, present in milk-fat, all contain an even number of carbon atoms, may be explained on the supposition that they are derived from one another by a process of  $\beta$ -oxidation. Many other examples of the helpfulness of this hypothesis might be cited.

It is of interest to note, that the possibility of the above-mentioned physiological reaction was doubted by chemists, owing to the fact, that such a reaction had not been observed in the chemical laboratory. The frequent observation of reactions and mechanisms in the living organism, which have not been hitherto observed, is certainly one of the stimulating attractions of biological research. This is especially true with regard to biochemical questions, since chemistry, perhaps more than any other science, has occupied itself with reactions, occurring in the test-tube without regard to natural processes. In many cases it is left to bio-chemistry to first unravel these intricacies by the investigation of natural objects. However, in the particular case, with which we are concerned, Dakin was able to assist in its development and also to show that the hitherto unobserved reaction might be successfully imitated in vitro. This change was brought about by hydrogen peroxide, an agent whose action frequently closely resembles that of the animal oxidizing agents.

After a general scheme for the metabolism of fatty acids had been established, a successful attempt was made to gain an insight into the mechanism of the breakdown of the amino-acids derived from proteins. This was done by using essentially the same method which had been helpful in the case of the fatty acids; that is to say, by the use of phenyl substituted homologues. The protein *Bausteine* or units are largely made up of amino-acids, all of which contain their nitrogen similarly linked to the  $\alpha$ -carbon atom. This nitrogen may be split off in the form of ammonia, leaving an  $\alpha$ -ketonic acid containing the radical—CO—COOH. The CO group, whether in the  $\alpha$  or  $\beta$  position, forms a *punctum minoris resistentie* for the attack of oxidizing agents. It follows, therefore, that one carbon atom is removed as the first stage in the oxidation of  $\alpha$ -ketonic acids, while the  $\beta$ -ketonic acids derived from the fatty acids part with two carbon atoms. Thus the amino-acids are converted into fatty acids, and these nitrogen-free radicals from proteins behave as fatty acids in their subsequent transformations.

In the course of these investigations upon fatty and amino-acid catabolism, the behavior of a large number of hypothetical intermediate products, including ketonic and hydroxy acids, unsaturated acids and acids with branched chains, etc., has been investigated and many valuable details have been discovered. Of these, I shall only mention the reduction processes by which ketonic acids are converted into hydroxy acids, and even into fatty acids. For these results form the chemical basis for the comprehension of fat formation from sugar, a reaction which must clearly necessitate far reaching reductions. Similar reactions lead to the reduction of acetoacetic acid to  $\beta$ -hydroxybutyric acid, and we now believe, with Dakin and others, that acetoacetic acid is the primary product from which  $\beta$ -hydroxybutyric acid is formed by secondary reduction. Formerly, the change was believed to be in inverse order.

One effect of these numerous discoveries has been to establish firmly the capacity of the animal organism for bringing about endothermic reactions, and furthermore, they have paved the way to a revision of many traditional theories. A principle long held by Pflüger that carbohydrates could originate only from carbohydrate substances has had to be abandoned, as the result of numerous experiments, particularly upon diabetics. For now we know that other food substances, such as protein, may yield carbohydrate, and American investigators have determined quantitatively the formation of sugar from a number of protein *Bausteine*.

The possibility of the reverse change, namely, the formation of protein from sugar and ammonia, was apparently excluded, for the statement that the nitrogen requirement of mammals could only be furnished by protein-like substances, was regarded as one of the most firmly founded dogmas of the old metabolic physiology. But in connection with the foregoing question, I should like to show how valuable for metabolic physiology an exact inquiry into chemical detail may be.

Every animal, even when overfed, constantly excretes in

the urine a certain amount of nitrogen, which is derived from cell protein used up as the result of cellular functions. During starvation, this nitrogen minimum rapidly reaches a constant value, and, until recently, it was believed that this could not be influenced by inorganic nitrogen but only by protein. When it came to be recognized that protein underwent a far reaching hydrolysis in the intestine, with the production of amino acids, it was inferred and subsequently proved that these latter substances could maintain the nitrogen equilibrium, that is, the balancing of the nitrogen output in the urine by the nitrogen containing substances of the food.

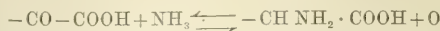
The capacity for synthesizing protein *Bausteine* from inorganic nitrogen was ascribed solely to plants and amino acids seemed to be the simplest substances capable of meeting the nitrogen requirements of animals. As a result of our knowledge of the breakdown of the amino acids, we are now in a position to admit this question to a revision. May not the organism, after all, be able to utilize inorganic nitrogen, that is to say, the same ammonia liberated by the breakdown of amino acids according to the first catabolic reaction already referred to?

The ammonia must, first of all, be brought in contact with substances which are formed simultaneously with it in the organism, such as ketonic acids. These experiments were successful, for it was found that the animal body can synthesize amino acids from ammonia and ketonic acids, into which they may be reconverted later. The catabolic reaction is evidently reversible. We must therefore abandon the conception of differences between plant and animal chemistry, based upon the supposed inability of the animal body to effect syntheses. Ammonia is constantly present in small quantities in the animal body, and  $\alpha$ -ketonic acids, which may react with it to give amino acids, originate, as we know, not from fatty acids, but from sugar. We know relatively little of the oxidative catabolism of sugar, but we do know that in one way or another, lactic acid and pyruvic acid may be formed, and that both of these may be combined with ammonia to form protein *Bausteine*, especially alanine.

We are now in a position to understand the protein sparing action of carbohydrates, while fatty acids yielding  $\beta$ -ketonic acids which are not convertible into protein *Bausteine*, have not the same action. Fact and theory agree. But now, if the reaction involving the liberation of ammonia from the amino acids is reversible, one would expect that the administration of ammonia would influence the synthesis and exert a protein sparing action. This theoretical deduction has been confirmed in a number of ways. Investigations by both clinicians and physiologists have shown that animals may be maintained almost in nitrogenous equilibrium for weeks at a time, with ammonia as their sole source of nitrogen. It would seem, therefore, as if the consumption of the protein material of the cells might be reduced almost to nothing, if only an excess of carbohydrates is administered.

I should like you to notice, how the exact investigation of

this single chemical reaction, and the demonstration of the short equation:



together with other similar researches in intermediary metabolism has entirely revolutionized the teachings of the investigations of the laborious older metabolic physiology. No clearer proof could be offered of the value of exact chemical analysis in biological research.

Thus we see how products of intermediary metabolism may react with one another; for example, those from amino acids with those from sugar. Doubtless also substances derived from fat, protein and carbohydrates may combine with one another. It appears probable that the synthesis of fat, following excessive consumption of other forms of food, may find its explanation in a process of reversible fatty acid catabolism. Possibly acetaldehyde or acetic acid compounds derivable from all of the three chief groups of food substances, may undergo condensation with formation of unsaturated or oxy compounds. These, in turn, may undergo reduction with formation of fatty acids with their long chain of carbon atoms. This type of reduction has already been observed in the case of benzoylpropionic acid and the corresponding unsaturated acids.

Another example of such a reaction has been noticed in connection with the synthesis of amino acids in the animal body. It was found that an acetic acid radical may attach itself to the nitrogen group, but we are not yet fully informed as to the origin of this acetyl group. It will be noticed that this aliphatic group is combined in precisely the same fashion as are phenylacetic and benzoic acids combined with glycocoll in hippuric and phenaceturic acids. It would seem as if we were dealing with a reaction of general significance. Just as in the proteins the acid carboxyl groups are combined as acyl radicals with the basic amino groups, so we may picture the acid end products of fatty acid oxidation combining with amino acids. Possibly our experiences with aromatic substances containing the benzoyl and phenacetyl groups may be found true in the case of their aliphatic homologues.

Whether the acyl radicals originate from the decomposition of sugar, for example pyruvic acid, or whether they come from acetoacetic acid, is capable of experimental determination by observing whether the yield of such condensation products is increased on feeding with fat or with carbohydrate. Should the mother substance of these acetyl groups prove to be the acetone bodies, which, as we know, do so much injury in the stages of acidosis in diabetes, it is possible that the feeding of easily acetylated substances may prove of therapeutic value. Such substances, perhaps might take up considerable quantities of these acids in the form of acetyl groups and thus make them less harmful. Such a line of research should be of direct interest to the practitioner of medicine.

The more we succeed in unravelling the details of the chemical mechanisms of the animal body by tracing the individual reactions, the more likely are we to investigate successfully what we may call the bypaths of metabolism in which sub-



stances undergo reactions for other purposes than simply a liberation of energy. It is surprising to note how the smallest derangement of chemical conditions in the body may result in far reaching injury.

We have a fairly clear picture of the reactions by which the pharmacologically active adrenalin may be formed from tyrosine. The change necessitates the splitting off of carbon dioxide, methylation and the introduction of two hydroxyl groups. It has recently been shown that a number of substances contained in ergot which have long been used therapeutically, may be derived from different protein *Bausteine* by a similar reaction leading to the removal of carbon dioxide. The close chemical relation between food substances and most powerful poisons, is very striking. It is through reactions such as these, that toxins and other noxious bacterial products may be formed.

Almost all manifestations of disease have a chemical basis. But can we hope to comprehend these when we know so little

of the normal chemical mechanisms of the organism? Every branch of medical science is calling chemistry to its aid—pathology, internal medicine, bacteriology and serology. Pediatrics has become largely a study of the chemical pathology of nutrition, and even in such subjects as diseases of women and nervous diseases, progress is sought by chemical methods. In the universities of the Old World, new branches of learning, anxious to throw off restraints, progress but slowly. They must develop, as a rule, from existing departments which, owing to their own limited resources, are often slow to lend a helping hand. Time is required to bring about the needed changes. In this country of unlimited possibilities, such restrictions need not be reckoned with and the favorable conditions we see here promise a development for our science that may soon rival that of Europe.

May our science and practical medicine flourish, and rising above all personal and national considerations, serve the great cause to which we are all devoted—the welfare of mankind.

## THE WASSERMANN REACTION IN THE JOHNS HOPKINS HOSPITAL.

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Since the application of the Bordet Gengou principle of complement fixation in the diagnosis of syphilis by Wassermann, Neisser, and Bruck, the vast number of reports from clinics all over the world have proved the great value of this method. The Wassermann Reaction has been extensively employed in The Johns Hopkins Hospital in the past four years, and our experience with it confirms the results of a host of workers as to its reliability and specificity as a diagnostic procedure. The first report upon its use in this clinic was made by Clough,<sup>1</sup> in 1910, and comprised observations extending throughout the year 1909. Since that time no report of the results in this clinic have been published. It was thought that perhaps a résumé of the more recent cases would prove of some interest, and at the suggestion of Professor Barker all the cases have been collected, upon which this reaction was done the past year, from September, 1911, to August, 1912.

The technique of this reaction is now so well known that a detailed description of it is quite unnecessary. In the main we adhere to the original technique described by Wassermann, Neisser, and Bruck, except that an alcoholic extract of fetal luetic liver instead of watery antigens, has been employed. While Wassermann,<sup>2</sup> as late as 1910, still maintained the superiority of watery extracts over alcoholic, yet Bruck<sup>3</sup> recommends alcoholic solutions as giving identical results. The greater stability of the alcoholic antigen is perhaps the strongest point in its favor, and has resulted in its supplanting, to a great measure, the watery antigens.

Following the discovery of Marie and Levaditi<sup>4</sup> and others, that extracts of normal guinea-pig's heart were able in the presence of syphilitic serum to fix complement, many workers

began to use such extracts as antigen. Further work, however, by Wassermann,<sup>5</sup> Plaut,<sup>6</sup> and Bruck<sup>1,c</sup> indicates that a specific antigen is superior to a non-specific one and gives a higher percentage of positive reactions in luetic cases. In this clinic the antigen employed is prepared from fetal syphilitic liver, which we have always been able to obtain and against which no worker has raised any objection. The liver is ground up, mixed with nine parts of absolute alcohol, shaken for twelve hours, allowed to remain in the thermostat at 37° C. for 48 hours, then filtered, and the clear filtrate used.

The patient's serum before using is inactivated at 56° C. for one-half hour, and anti-sheep rabbit serum plus sheep red corpuscles is employed as the hemolytic system. We have not had in this clinic any extensive experience with Noguchi's<sup>7</sup> modification of the Wassermann reaction, but feel that the work of Dean,<sup>8</sup> Bailey,<sup>9</sup> and others does not point to normal anti-sheep amboceptor as playing an important rôle in obscuring positive reactions.

As complement, fresh guinea-pig's serum diluted 1:10 is employed. The complement and amboceptor are titrated each time just before using—the *Vorprüfung*—and three or four times the titer of the amboceptor is employed for the final tests. The tubes are placed in a water bath at 37° C. for one-half hour to fix the complement, and then left in the bath for one hour to allow hemolysis to take place.

Since the introduction of the Wassermann reaction in this clinic, it has been employed as a diagnostic method in practically all cases giving a history at all suspicious of lues, and has also been used in a great many obscure cases where the diagnosis was in doubt.

During the past year, from September 1, 1911, to August 1, 1912, the Wassermann reaction has been performed upon the sera of 1200 patients, the great majority of whom were medical cases. This number includes a great variety of diseases ranging from outspoken cases of syphilis to neurasthenic patients, in whom the reaction was done for the purpose of excluding lues. This series includes a great variety of functional and organic nervous diseases, cardiac diseases, nephritis, diabetes, pneumonia, typhoid fever, gastro-intestinal diseases—in fact, almost every medical disease seen in an active clinic during the course of a year. A fairly large number of cases of brain tumor from Prof. Halsted's service have also been included.

Of these 1200 cases, 239, or 20 per cent, gave positive reactions; while 961, or 80 per cent, were negative. Of the cases giving positive reactions, 55, or 24 per cent (nearly one-fourth!), gave no history of a primary sore. The percentage of negroes in the above figures is of some interest. The Wassermann reaction was performed upon 185 negro patients, the great majority being cardiac or cardio-renal cases, but also including numerous other more uncommon diseases. Of this number, 61, or approximately 34 per cent, gave positive reactions; while 124, or 66 per cent, were negative. When this number is compared with the reactions on white patients, it is seen that 34 per cent of negroes compared with 17 per cent of whites, give a positive reaction. This indicates a frequency of positive reactions in negroes twice that of the whites. These figures do not perhaps give a sufficient indication of the greater frequency among negroes, since the total number of reactions performed on the sera of colored patients is considerably less than that on whites.

The results of the Wassermann reaction in certain diseases deserve separate comment.

#### AORTIC INSUFFICIENCY.

The Wassermann reaction in 42 cases of aortic insufficiency showed 21, or 50 per cent, positive reactions; while 21 were negative. Of the 21 negative cases, all but six gave a history of rheumatic fever, four of the six showed marked arteriosclerosis, and one patient included in the six died of an acute aortic endocarditis.

The above figures include both aortic insufficiency alone and in association with other heart lesions. The cases of pure aortic insufficiency show different results. Of 14 cases of pure aortic insufficiency, 13 were positive and only one negative. This patient with the negative reaction showed, however, partial fixation and gave a history of a primary sore twenty years before. This shows that in our series of pure aortic insufficiency, 93 per cent gave positive reactions, more striking figures than those of Citron,<sup>10</sup> who found that in 13 cases, 62 per cent gave positive reactions. Donath<sup>11</sup> found 90 per cent positive in 10 cases of pure aortic insufficiency, Longcope<sup>12</sup> found 81 per cent positive in 18 cases, and Collins and Sachs<sup>13</sup> saw 92 per cent positive in 13 cases.

#### ANEURYSM.

In this series the Wassermann reaction was applied in 22 cases of aneurysm, mostly of the aortic arch. Twenty-one, or 95 per cent, gave positive reactions. The patient who gave a negative reaction was a negro who had a definite history of syphilis seven years before. His serum was tested one month later after antiluetic treatment, and with the same result. Two of the cases were of some interest, one an aneurysm of the dorsalis pedis artery and the other a popliteal aneurysm. Seven of the 22 cases gave no history of lues.

This percentage of positive reactions is considerably higher than that obtained by Clough in the first communication from this clinic, who found only 50 per cent positive in 20 cases. The percentage, however, during the years 1909-1911 was much higher and about that obtained the past year. These figures are very impressive and bear out the conviction already held by most clinicians, as to the overwhelming, if not sole, importance of syphilis as the etiological factor in "spontaneous aneurysm."

#### TABES AND PARESIS.

The Wassermann reaction in 17 cases of tabes showed 11, or 64 per cent, positive and 6 negative. Three of these patients gave a negative Wassermann in the serum, while the cerebro-spinal fluid was positive; and three of the patients having positive reactions with their serum showed negative reactions in the cerebro-spinal fluid. Eight of the patients admitted luetic infection; 9 gave no history.

Thirteen cases of general paresis were tested. Twelve, or 92 per cent, of this number were positive. The cerebro-spinal fluid was positive in every case examined (seven), while the blood was negative in seven cases. Nine of the 13 gave a luetic history.

In addition to these diseases of the central nervous system, the reaction was applied to two cases of multiple sclerosis, one case of Friedreich's ataxia, three cases of progressive central muscular atrophy, two cases of bulbar paralysis, and 15 cases of "idiopathic" epilepsy; all with negative results.

#### BRAIN TUMOR.

This group of cases includes a variety of cerebral tumors—gliomata, hypophyseal tumors, and cysts, cerebellar tumors and cysts, and tumors of the spinal cord. The Wassermann reaction was done with the serum of 59 cases, all giving negative results. In seven of these cases the test was also negative with the cerebro-spinal fluid.

Newmark<sup>14</sup> has reported two cases with non-specific tumors of the central nervous system which gave positive reactions. One of these patients died and the tumor proved to be a gliosarcoma of the brain. A complete autopsy, however, was not permitted. The Wassermann reaction was also positive in the cerebro-spinal fluid taken at autopsy. The second patient gave a positive reaction in the blood and was given vigorous anti-luetic treatment despite which symptoms of compression

of the spinal cord increased. The reaction was positive in the cerebro-spinal fluid July, 1911, and on August 31, 1911, an intradural psammoma was removed. The Wassermann reaction was negative in the cerebro-spinal fluid during operation and in the patient's serum on September 18, 1911.

Neither of these cases proves that non-specific tumors of the central nervous system give positive reactions, since syphilis was not excluded in the first case and in the second case the vigorous anti-luetic treatment may have been sufficient to cause the disappearance of the positive reaction.

In this connection a case reported by Citron<sup>1c</sup> is of considerable interest. This patient was a case of cerebellar ataxia who gave a positive Wassermann. At autopsy the cause of the ataxia was found to be a softening (*Erweichungsherd*), and no signs of luetic changes were found in the brain. Upon further examination, however, the prosector found a well marked aortitis, which, although it had never manifested itself by any symptoms, was nevertheless quite characteristic, and the only definite evidence of luetic infection present.

One patient in our series, who gave a positive reaction with the cerebro-spinal fluid but negative in the blood, was operated upon because of certain symptoms (dizziness, poor vision, and impaired hearing) pointing possibly to a cerebral tumor. Operation, however, showed no tumor but only a chronic serous meningitis, probably of luetic origin.

#### DIABETES MELLITUS.

The Wassermann reaction upon the sera of ten diabetics showed eight negative reactions and two positive reactions. Of the two patients who gave positive reactions, one admitted a very recent luetic infection and the second patient, while denying lues, had, however, symptoms of *tabes dorsalis*.

#### PELLAGRA.

The Wassermann reaction was negative in four cases of pellagra. This number, while too small to admit of definite conclusions, yet agrees with the results of Fox,<sup>2</sup> Carletti,<sup>3</sup> and Vallardi,<sup>4</sup> who state that the Wassermann reaction is usually negative in pellagra.

#### JAUNDICE.

The interesting statement is made by Kaplan<sup>5</sup> that 18 sera containing bile products gave in his hands a positive reaction, although in most of them "syphilis could be absolutely excluded." In our series the Wassermann reaction was performed upon 14 sera from patients who were definitely jaundiced, many showing the most extreme degrees of jaundice. Two patients only of this number gave positive reactions. One of these patients had a gumma of the liver. The second patient, while giving no definite history of lues, had, however, probably been exposed to infection, and gave a markedly positive luetic reaction.

The causes of the jaundice were: Cirrhosis of the liver (seven cases), catarrhal jaundice (two cases), liver necrosis

(two cases), gumma of the liver (one case), carcinoma of the bile ducts (one case), and carcinoma of the head of the pancreas (one case).

#### THE WASSERMANN REACTION OF THE CADAVER.

Bruck,<sup>1c</sup> as is well known from the result of his tests with the sera of cadavers, is very sceptical of their value when positive, and expresses the conviction that *die Syphilisreaktion est ein rein biologisches Phänomen, aber kein kadaveröses*. He found that post mortem sera from patients who had died of various diseases gave positive reactions where the autopsy showed no signs of syphilis. Subsequent investigation of this question shows widely divergent views. Fraenkel and Much<sup>2</sup> found that reactions on cadaver serum corresponded with the pathological diagnosis. Nauwerck and Weichert,<sup>3</sup> as the result of investigations upon the sera of 200 cadavers, also found agreement between autopsy findings and post mortem serum reactions. They state that they have been unable to find any difference "between the living and the cadaver reaction." Krefling,<sup>4</sup> on the other hand, found positive reactions in the sera of cadavers who showed no post mortem signs of lues.

Some of these discrepancies may be due to placing too much reliance upon the post mortem examination, since it is quite possible for patients to have syphilis with a positive Wassermann, and yet present no recognizable lesions at autopsy. For this reason it seems quite necessary to perform the reaction upon the sera both before death and after death, and then by comparison to determine the value of the Wassermann reaction on the cadaver. Nauwerck and Weichert found agreement between 19 sera examined both ante mortem and post mortem, and Schmidt<sup>5</sup> obtained similar results in 32 cases.

The Wassermann reaction has been performed on the sera of 25 patients in this clinic, both before and after death. The serum from the cadaver was obtained by aspirating the heart under sterile precautions and was taken at different periods after death, varying from two hours to two days. The serum was then immediately placed on ice and every specimen was found satisfactory. In these 25 tests there was perfect agreement between ante mortem and post mortem results in every case but one. This patient, who had an abdominal aneurysm, gave a positive Wassermann on admission, but after death his serum showed no complement fixation. He had, however, been under strong antiluetic treatment during his stay in the hospital, which extended over a period of eight months. These results then, agree with those of Nauwerck and Weichert, and Schmidt, in showing the reliability of the test on the serum of cadavers.

#### SUMMARY.

The past year's experience with the Wassermann reaction in this clinic confirms our faith in the reliability and specificity of this reaction. The only other diseases in which positive reactions have been reported (trypanosomiasis, yaws, scarlet fever, leprosy, and possibly malaria) are either so



easily diagnosed or so uncommon here as to cause no confusion.

Wassermann<sup>5</sup> states that he and his assistants have performed over 10,000 examinations and never yet made a false diagnosis. While the number of patients in our series is much smaller, we feel that we have not made a false diagnosis the past year when the diagnosis of syphilis was placed after the names of 239 patients who showed a positive Wassermann reaction.

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## EXCESSIVE THICKENING OF THIERSCH GRAFTS CAUSED BY A COMPONENT OF SCARLET RED (AMIDOAZOTOLUOL).\*

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#### INTRODUCTION.

There has been some skepticism expressed at one time or another in regard to the power of epithelial stimulation claimed for certain of the organic coloring matters (Scarlet Red, Soudan III, Azodolen, Pellidol, etc.), when applied locally to granulating wounds.

To my mind this matter has been settled beyond a doubt, as, during the last four years a number of enthusiastic articles have been published by well-known investigators on the satisfactory use of these substances. These papers almost uniformly report splendid clinical results in hastening the healing of sluggish granulating wounds of varying etiology, and in every situation.

As is usual when a promising new therapeutic agent of this type is brought to the attention of the medical profession, it has been used by many who are not familiar with the principles of wound healing, and who have little knowledge of surgical dressings. If unfavorable results have been obtained by such individuals, I do not believe it is entirely due to the dyestuff.

I have found that these substances will not heal every wound, but, in the majority of instances, when applied with

the proper technic, they will cause epithelial stimulation in the edges of the most sluggish wounds, and give a rapid, stable healing.\*

The use of these coloring matters has also been objected to, by some who admit their power of epithelial stimulation, on the ground that there might be the possibility of producing epithelial overgrowths having malignant characteristics. It is a well-known fact that malignant degeneration may occur in any chronic ulcer, even though only the blandest dressings be used. The consensus of opinion, deduced from experimental and clinical work, is that there is no more danger of producing malignant growths by the clinical use of these substances than with any other dressing. My own experience in the treatment of a large number of cases has convinced me of this, and I feel no hesitation in using the organic coloring matters on proper wounds.

I take this opportunity of warning against the indiscriminate use of these substances by inexperienced persons, as considerable harm may be done with them by improperly applied, and too long continued, dressings. There is, occasionally, an overgrowth of epithelium following the use of these dyestuffs, even when the greatest care is exercised but, after discontinuing the stimulating dressing, this overgrowth soon assumes the level and appearance of the normal skin.

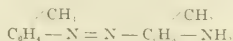
The following case shows the epithelial stimulating power of amidoazotoluol to a remarkable degree, and may be of interest:

#### HISTORY OF CASE.

*Admitted to the Union Protestant Infirmary, May 7, 1910.*  
*Diagnosis.*—Ulcers following burn.

\* Johns Hopkins Hosp. Bull., 1909, xx, 176. Ann. Surg., 1911, xxxviii, 702. Boston M. & S. J., 1912, clxvi, 891.

\* Amidoazotoluol is an amidoazo compound employed as an intermediate product, which, when combined with beta-naphthol, forms the Scarlet Red originally used, experimentally, by Fischer,<sup>1</sup> for the production of atypical epithelial proliferations; and was first used, clinically, by Schmieden.<sup>2</sup> Amidoazotoluol was first used clinically by Hayward.<sup>3</sup> It has the formula:



<sup>1</sup> München. med. Wehnschr., 1906, liii, 2041.

<sup>2</sup> Zentralbl. f. Chir., 1908, xxxv, 153.

<sup>3</sup> München. med. Wehnschr., 1909, lvi, 1836, and Deutsche Ztschr. f. Chir., 1911, cxii, 467.



FIG. 1.—Appearance on admission. Ulcer of right arm due to burn 6 months previously. Note exuberant, unhealthy granulations. Grafted skin can be seen on the forearm.

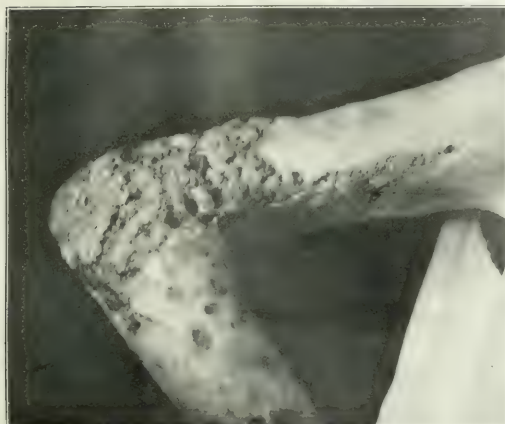


FIG. 2.—(a) Taken July 20, 1910. Note the marked thickening of the Thiersch grafts. The thickened grafts have begun to separate into irregular fungating masses which can be plainly seen.

(b) Taken August 1, 1910. Portions of the thickened grafts have assumed the level of the normal skin. Overgrowth can still be seen in other areas. Note the overgrowth which is attached only by its edges, beneath which a probe is passed. There are a number of similar areas scattered over the arm.



FIG. 3.—(a) Taken January 7, 1911. Five months after discharge. The skin is movable and, for the most part smooth, although several thickened areas can be found. There is considerable pigmentation.

(b) Taken January 4, 1912. Seventeen months after discharge. There is marked blotchy pigmentation of the grafted area. On careful examination of this skin, one or two small, flat thickened areas can be found. There are also a few minute depressions in the skin which are filled with comedo-like masses. Otherwise the skin is normal.





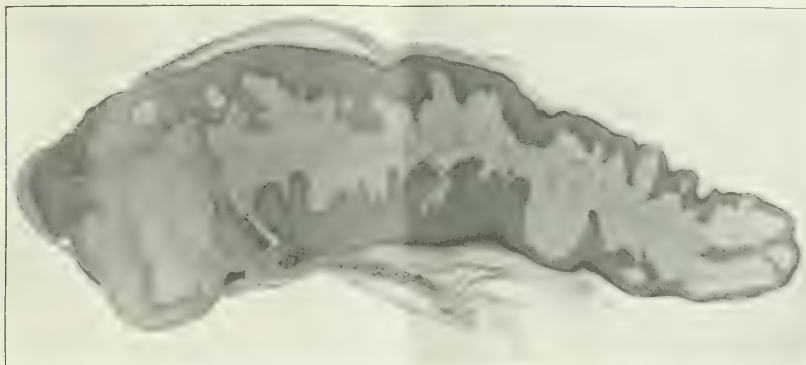


FIG. 4.—(Microphotograph by Schapiro. Zeiss. Obj. AA. Oc. 3.) Section of papillomatous overgrowth. For description see text.



FIG. 5.—(Microphotograph by Schapiro. Zeiss. Obj. AA. Oc. 3.) Section of papillomatous overgrowth. For description see text.



*Treatment.*—Thiersch grafting in conjunction with amidoazotoluol ointment.

*Clinical History.*—White man, aged 30 years, engineer.

*Family and Personal History.*—Unimportant.

*Present Illness.*—Six months before his admission the patient was severely burned in an oil explosion. The head, neck, both upper extremities and portions of the back and chest were involved, and his condition was serious. He was admitted to the Johns Hopkins Hospital in a critical condition and remained there for five months. While in the hospital skin grafting was resorted to a number of times, and considerable progress was made toward healing. He was discharged, at his own request, before healing was complete, and was referred to the Out-Patient Department for dressings. After several weeks his condition was unimproved, and, as the hospital was crowded, he was sent to the Union Protestant Infirmary, where he came under my care.

*Physical Examination.*—The patient was anemic and emaciated. There were large unhealed areas on the scalp and on both arms and forearms. I will describe only the ulcer on the right arm, as this is the particular wound to be considered in this report (Fig. 1).

An extensive granulating wound occupied the entire circumference of the lower two-thirds of the arm, including the elbow and upper two inches of the forearm. The wound extended three inches higher on the outer than on the inner side of the arm. On the inner side an area of skin previously grafted extended up from the forearm to the bend of the elbow. The granulations were exuberant, edematous and unhealthy. Practically all the skin of the forearm adjacent to the ulcer had been grafted before the patient came under my care. During the interval between admission to the Union Protestant Infirmary and operation on the right arm the other unhealed areas were grafted.

The granulations of this wound were brought into healthy condition by irrigations, free use of nitrate of silver, balsam of Peru, curved scissors, etc. At the same time very marked progress was also made toward healing by stimulating the wound edges with 4 per cent amidoazotoluol ointment, alternating every 24 to 48 hours with zinc oxide, or boric ointment. The newly formed skin edges were thick and stable, but showed no tendency to overgrowth. As the granulations were flat, firm and rose pink in color, in spite of the rapid stimulation of the wound edges, it seemed advisable to hasten the healing by grafting.

June 28, 1910. *Operation.*—Nitrous oxide-oxygen anesthesia.

A number of large thin Thiersch grafts were obtained from the left thigh by the method used at the Johns Hopkins Hospital,\* and the grafts were spread on protective and put aside. The thigh was dressed with boric ointment on protective, and the patient was allowed to regain consciousness. The granulating area on the arm was irrigated with salt solution and then dried carefully without causing bleeding. The grafts were buttonholed and applied over a large part of the unhealed area. Rubber impregnated mesh was placed snugly over the grafts, and over this overlapping strips of protective, dry gauze and a bandage.

June 30. The dressings were removed down to the rubber mesh, which was not disturbed. The grafted area was irrigated with normal salt solution and dressed with 4 per cent amidoazotoluol ointment on old linen, over the rubber mesh. This dressing was alternated with boric ointment every 24 hours.

July 12. (After six dressings with 4 per cent amidoazotoluol ointment.) The greater portion of the grafts had taken. Since the last note there had been a remarkable gradual thickening of all the grafts. The surface was smooth but rather uneven, and of a bluish grey color. The appearance was that of an edematous epithelial mass. The thickness varied between  $\frac{1}{4}$  and  $\frac{1}{2}$  of an inch. I felt convinced from my experience with occasional over-

growths of wound edges and other grafts caused by the organic coloring matters, that this thickening would begin to subside as soon as the stimulant should be removed. The thickened grafts were dressed with stearate of zinc powder and exposed to the air, in order to promote drying. The amidoazotoluol was discontinued. There was no excessive thickening of the wound edges.

July 20. The thickening of the grafts was still very marked, but the overgrowth had begun to separate into irregular-shaped fungating masses. When a section was removed for microscopic examination, there was little pain but profuse bleeding (Fig. 2).

July 22. Thiersch grafts from the left thigh were placed on the remaining undisturbed granulations and dressed with salt solution over the rubberized mesh.

July 29. All the grafts last applied had taken, and were of normal thickness, no amidoazotoluol having been used. The first grafts had resumed, in some places, the appearance of normal grafted skin. In others, several areas had assumed a papillomatous formation. Some of these were of the size of a pea, and were adherent to the underlying clear skin by a small pedicle. Others were flattened mushroom-like masses, with overhanging edges, while other areas were adherent here and there along their edges, and not elsewhere, so that an instrument could be passed freely underneath them. Some of the thickened areas were  $1\frac{1}{2}$  inches in diameter, a single portion comprising about one-half of this, and the rest being made up of closely set papillæ, which extended above the surface of the skin from  $\frac{1}{4}$  to  $\frac{1}{2}$  of an inch.

Several of these areas were cut off, and normal looking skin was found beneath, except for bleeding at the points of attachment. Here and there masses of cheesy secretion could be pressed from under the overgrown areas, and this had the typical odor of the contents of an atheromatous cyst. Microscopic examination showed this to be made up of epithelial debris.

August 13. Some of the papillary overgrowths had been removed, and many others had dried out and fallen off, as the blood supply of the pedicles was gradually occluded. Those which remained were much less prominent than at the last note. A large part of the thickened grafts had assumed the level of the normal skin, which was of a pinkish color. These level areas gave no evidence of having undergone excessive epithelial stimulation.

The patient was discharged in excellent physical condition, and with practically complete healing of all his lesions.

October 15. The greater part of the grafted skin on the right arm was smooth, but here and there were scattered a few small flat, dry papillomatous overgrowths. These growths received their nourishment through very small pedicles, between which the formation was bridged. The patient was working at his usual occupation.

January 7, 1911. Practically all of the papillomatous growths had disappeared, and the area was covered with smooth, solid skin (Fig. 3).

January 14, 1912. The arm was covered with a stable, movable skin, which was heavily pigmented. On careful examination one or two very small thickened areas could be found on the inner side of the arm. There were also several comedo-like masses which filled minute pockets in the skin.

January 5, 1913. The condition of the skin had not changed since the last note.

*Histology.*—(Microscopic examination by Dr. Joseph C. Bloodgood\*) (Fig. 4). There was an oblong piece of tissue with a central zone of edematous connective tissue surrounded by epidermis. The papillary bodies of the epidermis were present. These papillary bodies varied in size and shape; they were larger and more irregular than in the normal epidermis. In some places the hornified epithelium on the surface was more marked than normal.

\*I take this opportunity of thanking Dr. Bloodgood for the microscopic study.



Corresponding to these areas the epidermis was thicker than in areas in which the hornification was less. The epidermis differed from normal in the fact that the basal cell was not so distinct in its morphology, and in places the downgrowth of epidermal epithelium was more irregular than normal. We would speak of it as atypical. In one end of the section the central connective tissue looked myxomatous or edematous. In the faintly stained intercellular substance there were a few round and stellate connective tissue cells, resembling, therefore, myxomatous tissue. Here and there was a lymph vessel filled with leucocytes. At the other end of the section there was a defect in the epidermal covering, and this was filled with lymphoid-cell granulation tissue. This granulation tissue grew out from a narrow isthmus in the epidermis, and projected over the surface of the epidermis, like a fungous ulcer. On each side of the granulation tissue in the defect in the epidermis, the epithelial cells were extending irregularly into the granulation tissue. The cell proliferation in the granulation tissue was of the type of the transitional and squamous cell. This histological picture was somewhat similar to that seen in the beginning of carcinoma.

The other piece of tissue (Fig. 5) had the appearance of having been cut on the bias. The central zone of connective tissue was smaller, the epidermis much thicker, and the section seemed to be horizontal through the papillæ rather than vertical. There were also a few cavity formations in the epidermis, filled with hornified epithelium, which had the appearance of the so-called inclusion dermoid cysts. In the connective tissue of this section, there were numerous endothelium-lined canals filled with blood, probably young capillaries, and some more dilated similarly lined spaces filled with blood, which may have been veins. There were also some dilated endothelium-lined spaces which suggest lymphatics.

The entire picture, therefore, suggests unusual epithelial activity. That is, the healing process of epidermization was going on very actively; one would naturally conclude, perhaps too actively, or, as Adami would express it, "over-sufficient." The possibility of producing a definite malignant epithelial growth from such stimulation, as has been observed in x-ray and radium keratosis, should be borne in mind. This possibility is illustrated in the character of the epithelial overgrowth into the granulation tissue filling a defect in the epidermis as noted above. Here the cells were not growing as in normal epidermization in which the downgrowth was always composed first of a basal-cell layer, but, instead, the transitional and squamous cells were proliferating irregularly into the granulation tissue, as in carcinoma. But these cells as yet have not assumed the abnormal morphology seen in cancer.

## REMARKS.

The microphotographs, especially Fig. 5, show a condition which resembles very closely the sections of the atypical epithelial proliferations produced by injecting scarlet red oil, subcutaneously, under pressure into a rabbit's ear.\* These experimental tumors never show a tendency to independent aftergrowth, and persist only as long as the injections are continued and the scarlet red remains in the tissues.

The epithelium of this patient seemed to be particularly responsive to the stimulation of amidoazotoluol, and these thickened grafts present the most remarkable condition of overgrowth which has come under my observation.

It is interesting to note that Thiersch grafts which were subsequently applied to unhealed portions of the same wound, under exactly the same conditions, but without being dressed with amidoazotoluol, were not thickened.

There was also great thickening of the deep pinch grafts placed on the undisturbed granulations of the ulcer on the scalp, which had been treated with amidoazotoluol before and after the application of the grafts. There was no such thickening, however, of similar grafts placed on undisturbed granulations, when not dressed with amidoazotoluol. There was distinct overgrowth of epithelium "pebbly formation" on the thigh, when the area from which the Thiersch grafts were removed was dressed with amidoazotoluol ointment. Another area on the thigh from which Thiersch grafts were taken, but which was dressed with boric ointment, showed no "pebbly formation."

The patient has been under observation for over two years and a half since his discharge from the hospital, and there is no sign of malignant degeneration anywhere.

This condition is unique, and I can find no report in the literature of a similar case. It demonstrates beyond a doubt the epithelial stimulating power of amidoazotoluol. It also seems to show that although this stimulation is excessive, there is no tendency to subsequent malignant degeneration.

\* F. H. Helmholz. Johns Hopkins Hosp. Bull., 1907, xviii, 365. Fig. 2, Exp. Ia.

## THE SUBSEQUENT HISTORY OF ONE THOUSAND PATIENTS WHO RECEIVED TUBERCULIN TESTS.

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In the Archives of Internal Medicine (1910, VI, 690) Hamman and Wolman reported the results of the application of the cutaneous and conjunctival tuberculin tests to one thousand patients coming to the Phipps Dispensary for Tuberculosis of The Johns Hopkins Hospital. From an analysis of the results certain conclusions were drawn as to the value of these tests in diagnosis. For this purpose the patients were divided

into six groups, the division being made upon the clinical evidence without reference to the outcome of the tests. It is important for a proper appreciation of the present study to bear in mind the data upon which the classification rested and the data are therefore repeated.

GROUP I. *Non-tuberculous*.—This group included those patients who had no symptoms or signs of tuberculous disease,

and those with symptoms which might have been readily accounted for by some disease other than tuberculosis.

**GROUP II. *Doubtful.***—This group included the patients presenting symptoms or physical signs that might be due to tuberculosis and for which no other satisfactory explanation could be given. The symptoms and signs, however, were not sufficiently convincing to establish the diagnosis definitely.

**GROUP III. *Probable.***—This group included patients with symptoms or physical signs so suggestive of tuberculous disease that clinically the diagnosis was in every way reasonable. However, complete confirmation had not been possible. We made a special group of these patients to free the incipient group as far as possible from the influence of the personal equation.

**GROUPS IV, V AND VI.**—These groups included the definitely tuberculous cases. As tuberculous were included cases with tubercle bacilli in the sputum and those affording only the strongest clinical evidence of tuberculosis. Cases about which clinical observers might have even a slight doubt were placed in the doubtful class which was therefore very large. The tuberculous cases were divided into incipient, moderately advanced and far advanced, according to the demands of the classification proposed by the National Association for the Study and Prevention of Tuberculosis.

It is important to add further that the examinations upon which the diagnoses in the one thousand cases were based were made in a busy out-patient department by a staff of twelve physicians. Some of these physicians possess experience and skill in the diagnosis of pulmonary tuberculosis far above the average, while a few have these qualities in but a mediocre degree. The classification, therefore, is not to be viewed as the interpretation of physicians of exceptional insight and finesse.

Our object in seeking the after history of these individuals tested with tuberculin was to throw light upon a number of points connected with the dispensary work. In the first place it might serve as further evidence of the value of the tuberculin tests. Many of the doubtful cases reacted to tuberculin. Has a larger percentage of those who reacted become manifestly tuberculous than of those who failed to react? Again, it has been suggested that in tuberculous patients the presence or absence, indeed the intensity of the tuberculin reaction, has important prognostic significance. The relation of the tests to the patient's condition two years later would settle this point. Yet again, it would furnish the opportunity to repeat the tests upon a large number of patients and thus determine the duration of the hypersensitiveness occasioned by a conjunctival instillation. But most important of all, we wished to use the subsequent history of tested patients as a control of the classification itself. A few words of explanation are necessary in this connection.

There is as wide an individual difference of opinion as of skill in the diagnosis of early pulmonary tuberculosis. Although a number of observers may be in accord upon the clinical evidence, still they may differ widely in the interpretation put upon it. A patient with suggestive symptoms and suggestive physical signs will be classed uncompromisingly as tuberculous

by one, as possibly tuberculous by another, as not tuberculous by a third. By "tuberculous," we mean a clinical not an anatomical diagnosis, and imply the therapeutic consequences that flow from the diagnosis: namely, if tuberculous the patient needs energetic treatment, preferably admission to a sanatorium; if doubtful, careful and prolonged observation; if not tuberculous, dismissal. Inclination to accept or urge one of these three diagnoses represents a certain attitude towards tuberculosis work and is greatly influenced by mental bias. A number of physicians are sceptical of and some irritated by the diagnostic refinements of tuberculosis workers. They miss the spirit of the work and therefore misinterpret its aim. They will have none of the ultra-refined specialism, and the symptoms and lesions must be gross before they bend their stubborn judgment. Unquestionably helpful diagnoses are thus overlooked. At the other extreme stand many sanatorium physicians. To obtain satisfactory results from treatment they justly clamor for early cases, and their zeal and enthusiasm naturally color their judgment. They lean upon a forceful argument, for in the presence of indefinite symptoms and signs it is safer to say a patient has tuberculosis and then cure him with six months' treatment in a sanatorium than to hesitate and later find, perhaps, that valuable time has been lost. It can do no harm, they urge, to treat a few patients needlessly if thereby you prevent hundreds of others from going on to hopelessly advanced disease. We will not stop to analyze these arguments which are interesting in many ways. We merely suggest that a possible fallacy lurks behind the "few." Between these two extremes stands the large body of destructive tuberculosis students. They do not see advancing destruction lurking behind each slightly impaired percussion note, each rude inspiration, and yet experience has taught them to be wary and circumspect in judging. They demand reasonable proof before they pronounce a patient tuberculous while they regard every unusual feature with grave suspicion. Indeed, they are so permeated with suspicion that they naively transfer this attitude to the patients and speak of them as "suspicious," thus clothing with their own mental bias many entirely unsuspecting and confiding individuals.

We have fought out this question in the Tuberculosis Dispensary during the past eight years, and as a whole we have come to assume a very conservative attitude towards the early diagnosis of pulmonary tuberculosis. Our large group of doubtful or suspicious cases attests this. If, then, a large number of our doubtful cases have subsequently become manifestly tuberculous, we have erred on the side of being too conservative; whereas if, under the ordinary conditions of life, nearly all have remained well or have not become more definitely tuberculous than they were before, our standpoint is entirely justified. Without knowing the results of this investigation, we may at once predict that a certain number of the doubtful cases have become tuberculous. Many of the patients were seen only once, and then often hurriedly, and as we have before remarked, some of the examinations were not unusually skilful. Although all the diagnoses were carefully reviewed, it is often difficult to reach a satisfactory conclusion from the data furnished by another especially when, as was often the case, these

data are incomplete. To keep our tuberculous group as irreplaceable as possible we have made it a rule to place in the doubtful group any case not frankly tuberculous. It therefore includes many cases that would have been diagnosed definitely tuberculous had they returned for further observation.

The patients were sought by personal visits and by letter. Our nurses were indefatigable in their efforts to trace as many of the patients as possible and we wish to thank Miss Gould and Miss Donaldson, of the dispensary staff, and Miss LaMotte, directress of the municipal tuberculosis nurses, for their enthusiastic aid.

TABLE I.—THE PRESENT CONDITION OF 632 PATIENTS CLASSIFIED FROM THREE TO FOUR YEARS BEFORE.

	Sought.	Re-ports.	Well.	Not im-proved.	Became tuberculous.		Death not from tuber-culosis.
					Living.	Dead.	
Not tubercu-...	188	110	72—65%	37—28%	3—2.7%	1—0.9%	3—2.7%
Doubtful...	424	258	176—68	67—22	7—2.7	0—3.5	9—3.5
Probable...	78	47	29—61	.....	11—23	7—13	.....
Tuberculous							
Stage I....	35	21	13—62	4—19	.....	3—14	1—4.7
Stage II....	74	47	15—32	10—21	.....	22—47	.....
Stage III...	191	149	11—7	10—6.7	.....	128—86	.....

Table I shows the general results of the investigation. It will be noted that of 110 patients originally classified as non-tuberculous from whom reports have been obtained, four have become definitely tuberculous. A very brief account of these cases is given.

No. 3560, L. L., white male, aged 11 years, came to the dispensary on November 4, 1908, complaining of cough and loss of weight. Family history was negative, and there was no history of exposure to tuberculosis. Child had had whooping-cough, measles, chicken-pox and mumps and frequent attacks of bronchitis.

Present illness began on October 27, 1908, with cough and fever. He was in bed two days and then gradually grew better.

Patient was a fairly well nourished boy of delicate appearance. The cervical glands were just palpable. There was slight impairment at the right apex, with roughened breath sounds and prolonged expiration; no râles heard. Heart and abdomen were negative.

The 1 per cent and the 5 per cent conjunctival and the cutaneous tests were all negative.

Patient returned to the dispensary on January 25, 1912, saying that he had been well since his previous visit, except that for three years there had been a swelling in the left side of the neck. This grew larger and smaller at intervals.

The examination of the chest showed the same slight signs at the right apex as before.

Throat examination showed the presence of adenoids and enlarged tonsils. A surgical consultation agreed with the diagnosis of tuberculous cervical glands.

The 1 per cent conjunctival and the cutaneous tests were positive. Wassermann reaction negative. X-ray examination showed marked mediastinitis, but no definite pulmonary lesion.

No. 4634, R. R., colored girl, aged 15 years, came to the dispensary on July 9, 1909, complaining of cough. Family history, as far as it could be obtained, was negative. There was no history of exposure to tuberculosis. The past history gave nothing of importance in relation to the illness. Six years before admission the patient had had a cough, for which she had been treated in the dispensary. The cough subsided and she was then well until three weeks before admission, when the cough returned.

Examination showed a well nourished colored girl, with slightly

enlarged cervical glands, marked pyorrhea alveolaris and enlarged tonsils. The lungs showed slight impairment above and below the right clavicle and in the supraspinous fossa. Breath sounds over this area were rough and expiration prolonged. Numerous coarse, moist râles and a small number of fine râles heard over the whole side. Over the left back there was slight impairment below the angle of the scapula and numerous fine moist râles over the area of impairment. Examination otherwise negative.

The 1 per cent and the 5 per cent conjunctival and the cutaneous tests were negative.

At the end of a month, the râles had completely disappeared, and the slight impairment above and below the right clavicle and in the right supraspinous fossa was the only abnormality made out on examination.

Patient returned to the dispensary on May 3, 1911, with pleural effusion on the left side.

No. 4835, E. P., white woman, aged 52 years, came to the dispensary for examination on August 20, 1909, because she had been nursing a tuberculous patient for 13 months. She had had a little cough occasionally. Family history and past history were negative. Had always been a healthy woman.

Examination showed a well nourished woman, with indefinite signs at the right apex, namely, slight dulness and roughened breath sounds.

The 1 per cent and 5 per cent conjunctival and the cutaneous tests were negative.

Patient returned to the dispensary on October 3, 1910, having lost a few pounds in weight and feeling generally not so well as at the first visit.

Examination showed an advanced tuberculous lesion, involving both lungs.

Patient entered the State Sanatorium. She died of pulmonary tuberculosis on December 27, 1911.

No. 5072, J. B., white male, aged 39 years, came to the dispensary on November 10, 1909, complaining of nose trouble. One brother had died of tuberculosis. He had been exposed to the disease in his workshop. He had been always healthy. For many years he had had nasal catarrh, and some cough and expectoration.

Patient was a fairly well nourished man, in good general condition.

Examination showed slight impairment above and below the right clavicle and in the supraspinous fossa. Breath sounds were rather suppressed and a few fine râles were heard scattered over the upper front and back. The percussion note was impaired on the left side, above and below the clavicle and in the supraspinous fossa. Breathing was very distant and suppressed. A few fine râles at the third rib in front and over the upper back.

The 1 per cent and 5 per cent conjunctival tests were negative; the cutaneous test positive.

The pulmonary condition was considered to be emphysema and chronic bronchitis, and as the nasal symptoms predominated, the patient was sent to the throat physician for operation. Examination showed a deflected septum with hypertrophy of both turbinates, largely obliterating the nasal cavity.

Patient returned to the dispensary on September 7, 1912. After his first visit he had had cough and expectoration at intervals. The nasal symptoms had not been completely relieved by the operation.

Examination showed that the impairment and change in breath sounds made out at the first examination had increased and the number of râles had also increased. The 5 per cent conjunctival and the cutaneous tests were markedly positive. The sputum contained tubercle bacilli. Patient's general condition was good. Was admitted to a sanatorium.

In the group classified as doubtful, 16 of the 258 patients of whom we have reports have become definitely tuberculous.



We have shown a special interest in this group and to make the nature of these cases clear we briefly state the facts concerning them.

No. 2352, M. M., white female, aged 52 years, came to the dispensary on January 10, 1908, complaining of bronchial trouble. Family history was negative. Patient had had pleurisy 12 years before; had had bronchitis, with cough, expectoration and dyspnea for many years. Symptoms had been getting worse for a year before admission. Patient's general condition was satisfactory.

Examination of the lungs showed impairment over both upper lobes, with diminished intensity of the breath sounds and blowing expiration. Numerous sonorous and sibilant râles over both sides.

Three sputum examinations were negative. The 1 per cent conjunctival test was negative; the cutaneous test, positive.

The case was regarded as one of chronic bronchitis, with tuberculosis as a possibility.

Patient returned to the dispensary in May, 1912. Although the general condition had remained good, examination at this time showed marked bilateral tuberculous involvement. The 1 per cent conjunctival and the cutaneous tests were positive.

No. 3404, M. C., white female, aged 63 years, came to the dispensary on September 24, 1908, complaining of cough that had been present, off and on for several years. The family history was negative. The daughter-in-law had tuberculosis. Nothing of interest in the past history.

The patient was a fairly well nourished old woman, seven pounds under weight.

The lungs showed impairment above and below the right clavicle and in the supraspinous fossa, with harsh exaggerated breath sounds, and a few fine râles above and below the clavicle. Numerous sonorous and sibilant râles throughout both lungs.

One sputum examination was negative. The 1 per cent conjunctival test was negative, the 5 per cent conjunctival and the cutaneous tests were positive. The case was diagnosed as bronchitis probably with pulmonary tuberculosis.

The patient came to the dispensary off and on during the following year. On April 3, 1912, she had lost ten more pounds in weight, cough was more troublesome than it had been and examination showed a definite increase in the pulmonary lesion, with numerous moist râles.

August, 1912. The 1 per cent conjunctival test was positive. Patient still comes to the dispensary and is in fairly good condition.

No. 3524, L. M., white female, aged 41 years, came to the dispensary on October 23, 1908, complaining of pain in chest and back, and slight cough. Family history was negative. Patient had been helping to nurse a tuberculous patient. She had had measles and rheumatism. She was rather thin and pale and six pounds under weight.

Examination showed dulness over right upper front to second rib with increased transmission of voice sounds and moist râles from the second to the fourth rib. On the left, the note was impaired to the third rib, the breath sounds blowing and fine râles above and below the clavicle and at the base.

The sputum examinations were negative. The 1 per cent conjunctival and the cutaneous tests were negative. Diagnosis of probably pulmonary tuberculosis was made.

Examination on November 3, 1911, showed an extensive bilateral tuberculous lesion. Patient had tubercle bacilli in sputum, and the 1 per cent conjunctival test was positive.

No. 3552, J. N., white male, aged 74 years, came to the dispensary on October 30, 1908, complaining of sore throat and cough. Had always been a healthy man. Illness began three months before coming to the dispensary, with hoarseness, cough, profuse expectoration and loss of weight.

The patient was an emaciated old man, with the physical signs of emphysema and bronchitis, without signs of localized disease. The 1 per cent conjunctival test was positive.

Patient made but two visits to the dispensary, and was then lost track of. On June 6, 1912, the nurse reported that patient had died two years previously of pulmonary tuberculosis.

No. 3621, R. R., white female, aged 15 years, came to the dispensary on November 17, 1908, complaining of being nervous and easily tired. Patient spoke English with difficulty, so no satisfactory history could be obtained; however, she had apparently been well until one month before. She had no cough or expectoration.

Patient was of healthy appearance, and no definite signs of pulmonary disease were made out. The 1 per cent conjunctival and the cutaneous tests were positive.

On May 5, 1911, patient returned to the dispensary, complaining of loss of appetite, cough and sweating. She had lost five pounds in weight and examination showed impairment at the right apex, with modified breath sounds and a few râles after coughing.

Patient was subsequently admitted to a sanatorium and left much improved. She now has signs of a bilateral apical lesion, and symptoms pointing to hyperthyroidism.

No. 3813, H. S., white female, aged 33 years, came to the dispensary on January 13, 1909, complaining of stomach trouble. There was no history of tuberculosis in family. Past history of patient not important. She had been ill one year with pain in the stomach, poor appetite and growing weakness. She was a pale, nervous woman, with rapid pulse.

Pulmonary examination showed some impairment at both apices, with harsh breathing, and a few râles at the left apex.

Abdomen was somewhat distended and very tender, but no satisfactory abdominal examination was made at that time.

The 1 per cent conjunctival test was negative, the cutaneous test positive.

Subsequently patient was admitted to the hospital, where a diagnosis of tuberculous peritonitis was made.

Patient died on October 10, 1909.

No. 3847, W. B., colored man, aged 37 years, came to the dispensary on January 22, 1909, complaining of cough, pain in chest, and hemoptysis. Family and past history not important. His symptoms began six months before coming to the dispensary, following a cold.

Examination on admission showed marked involvement of the right upper lobe.

Two sputum examinations were negative. The 1 per cent conjunctival test was negative, the cutaneous test positive.

Patient continued coming to the dispensary, the signs of pulmonary involvement increased, and in September, 1910, there was definite tuberculous involvement of both lungs.

Patient died in February, 1912, no doubt of pulmonary tuberculosis.

No. 4033, R. K., white female, aged 27 years, came to the dispensary complaining of pain in the left side and blood spitting. Family history and past history were unimportant. Had always been a healthy girl.

Two weeks before coming to the dispensary, after drinking a glass of cold water, patient spat up a little blood. She had had no cough and no expectoration.

Patient was a well nourished girl of normal weight, showing no abnormality on examination other than a few râles in the left inter-scapular area.

Two sputum examinations were negative. The 1 per cent conjunctival and the cutaneous tests were positive.

The patient made no further visits to the dispensary and although requested to return for observation, refused to do so, saying that she was quite well, had gained in weight and was working hard. She continued to feel well until March, 1912, when

she had grip. She returned for examination in May, 1912, showing a marked involvement of the right upper lobe and a slight lesion in the left upper lobe. Tubercle bacilli were found in the sputum.

No. 4561, P. P., white female, aged 25 years, came to the dispensary on June 22, 1908. She came for examination, saying she had absolutely no pulmonary symptoms.

She was a well nourished woman. Examination showed impairment above and below both clavicles and in the supraspinous fossæ with prolonged, blowing expiration, and fine râles above and below the clavicles.

The 1 per cent and the 5 per cent conjunctival tests were negative.

The note was made: "One would certainly conclude from the signs that patient has a biapical tuberculous lesion. Absence of all symptoms and of tuberculin hypersensitiveness do not lend strong support to this view."

On April 29, 1911, patient again came for examination and the pulmonary signs were more definite than at the first examination. The 5 per cent conjunctival test was positive.

Patient has remained in good condition. She has had no sputum for examination.

No. 4685, H. S., white male, aged 21 years, came to the dispensary on July 19, 1909, complaining of cough. Nothing of importance in the family or past history. He dated his illness from four months before admission when he had caught a cold. He had been coughing since then, and had lost some weight.

The patient was emaciated and pale, and showed physical signs indicating a lesion in both the left and the right upper lobes.

The 1 per cent and the 5 per cent conjunctival tests were negative, the cutaneous test positive.

A diagnosis of probably pulmonary tuberculosis was made. condition marked "far advanced" and prognosis "bad". On February 15, 1912, a report was received, stating that the patient had died of tuberculosis one year before.

No. 4642, R. D., colored man, aged 46 years, came to the dispensary on July 12, 1909, complaining of cough, shortness of breath, dizziness and hemoptysis. He had been ill for two weeks.

He was rather poorly nourished and dyspnoic and showed a pleural rub at the left base. The lung examination was otherwise negative.

The 1 per cent and the 5 per cent conjunctival tests were negative, the cutaneous test positive.

On September 15, 1911, patient returned to the dispensary, having been fairly well until six weeks before. At that time, cough and expectoration became well marked, and he had fever, chills and dyspnoea. Respirations were very rapid and labored.

Pulmonary examination showed marked involvement of both upper lobes. Tubercle bacilli were found in the sputum.

No. 4690, H. W., colored man, aged 35 years, came to the dispensary on July 19, 1909, complaining of throat trouble and loss of voice. He had had cough and expectoration for six months. He was fairly well nourished, had a temperature of 100.8°F., and pulmonary examination showed incomplete consolidation of the right upper lobe with few râles.

The 1 per cent conjunctival test was negative, the 5 per cent conjunctival and the cutaneous tests, positive.

The patient made no further visits to the dispensary.

A report states he died of pulmonary tuberculosis November 29, 1909.

No. 4886, R. C., colored man, aged 27 years, came to the dispensary on September 7, 1909, complaining of shortness of breath and cough. Symptoms had been present for four months.

Examination showed a well nourished colored man of healthy appearance, with a little apical impairment, harsh breathing, and numerous moist râles over both chests. A diagnosis of chronic bronchitis was made, possibly with tuberculosis.

The 1 per cent conjunctival and the cutaneous tests were negative.

The patient made no further visits to the dispensary, but the nurse reports that he died in January, 1910, having had hæmorrhages and a bad cough.

No. 4904, M. B., white man, aged 67 years, came to the dispensary on September 14, 1904, complaining of pain in the abdomen. He had had cough and expectoration for some time; the abdominal pain was of 12 weeks duration.

He was an emaciated man, showing on examination bilateral apical impairment, with blowing breath sounds, and a few coarse, moist râles over both fronts. The case was diagnosed bronchitis, and probably pulmonary tuberculosis.

Two sputum examinations were negative. The 1 per cent and the 5 per cent conjunctival and the cutaneous tests were all negative.

Patient made several visits to the dispensary, gained in weight and said that the symptoms had been relieved.

Nurse reports that patient died of pulmonary tuberculosis in January, 1912.

No. 4923, F. W., white female, aged 14 years, came to the dispensary on September 20, 1909, complaining of cough and night sweats. She had had a cough for one month.

Examination showed some impairment over the right upper lobe, with coarse dry râles throughout the right side.

The 1 per cent conjunctival test and the cutaneous test were positive.

Patient reported one week later, saying that she felt much better. There is no further note until the report from the nurse, which states that the patient died of pulmonary tuberculosis in April, 1910.

No. 4934, E. W., white female, aged 38 years, came to the dispensary on September 23, 1909, complaining of cough. She had had cough off and on for a great many years. Nothing of importance in family or past history.

The patient was a well nourished woman, and looked to be fairly healthy. Pulmonary examination showed a little impairment over the right upper lobe, with suppressed breath sounds, and slightly blowing expiration. A few coarse râles were heard generally over the right side. A provisional diagnosis of chronic bronchitis was made.

The 1 per cent and the 5 per cent conjunctival and the cutaneous tests were all negative.

On September 29, she complained of soreness in the throat. A laryngeal examination was made on October 13, and a diagnosis of laryngeal tuberculosis made.

Patient died of pulmonary tuberculosis on April 10, 1911.

It is apparent that the diagnostic errors here recorded are due in most instances to errors in the interpretation of symptoms and physical signs rather than to a lack of ability in eliciting the signs. The wonder is that in some of the cases (Nos. 3524, 3847, 4685, 4690) there was any hesitation about classifying them at once as tuberculous. The occasion for such hesitation is not apparent in the records, but at the time there must have been some ground for it. Only two of the cases (Nos. 3621, 4023) presented such slight objective evidence of pulmonary disease that in spite of the symptoms the diagnosis was held open. Note the six times repeated classical error of calling a chronic pulmonary tuberculosis in the aged, chronic bronchitis. (Nos. 2352, 3404, 3552, 4886, 4904, 4934.)

We need make no other comment upon these cases than to add that to our mind the after history of our doubtful group fully substantiates the conservative attitude we have taken towards the early diagnosis of pulmonary tuberculosis. The

early diagnosis of pulmonary tuberculosis is more a matter of clinical experience and judgment than of unusual skill in eliciting slight abnormalities in the pulmonary physical signs. Whereas skilful pulmonary examinations require a natural gift that has been cultivated by assiduous application, the observation of symptoms needs only the training that every careful physician acquires in his daily work. It seems to us, therefore, that in attempting to improve the diagnostic acumen of general practitioners towards pulmonary tuberculosis, more emphasis should be laid upon the observation of symptoms than upon the pulmonary examination. To carry out the former is within the reach of all, while to do well the latter will ever be a goal unattained by most of them. It should be urged particularly that when obvious symptoms are present their importance be not subverted by a so-called negative examination.

In the probable and incipient groups it will be noted the same proportion of cases in each group are well and have died of tuberculosis. This we anticipated, since, as we have stated, we devised the probable group as an expedient for cases that we regarded as early pulmonary tuberculosis, but where the evidence for the presence of the disease was not convincing. We may assume from the after history of the patients in the two groups that nearly all of the probable cases were in fact instances of early pulmonary tuberculosis.

It will be seen that many of the patients who had definite tuberculous disease are classed as well. By well, we mean that the patients report that they feel well. It is not to be understood in any sense as meaning that they are cured. Perhaps a few examples will make the matter clear.

No. 964, J. G., white male, aged 22 years, came to the dispensary on July 22, 1906, complaining of cough and pain in the chest. Illness had begun five years before, with hæmorrhages. His father had died of tuberculosis.

The patient was a fairly well nourished man, without marked constitutional symptoms. There was involvement of most of the right lung. Tubercle bacilli were found in the sputum.

On November 9, 1909, examination showed that the process had extended to the left side, the whole upper left lobe being involved. The general condition had suffered, he was pale and had lost weight.

The 1 per cent conjunctival test and the cutaneous test were both positive.

Patient was admitted to Eudowood Sanatorium, and after discharge from the sanatorium worked at the Farm Colony until February, 1912. He was then discharged from the institution as arrested.

No. 4885, A. P., white male, aged 25 years, came to the dispensary on September 7, 1909, complaining of blood spitting. He had had cough off and on for a year.

The patient was a pale, thin man, 16 pounds under weight. There was involvement of both upper lobes, and a large portion of the right lower lobe.

The 1 per cent conjunctival test was negative, the 5 per cent conjunctival and the cutaneous tests were positive. Tubercle bacilli were found in the sputum.

Patient was put to bed until temperature came to normal, and then started on tuberculin treatment. There was some improvement in the general condition and in the physical signs. Fewer râles were heard in the lungs.

In May, 1911, he entered Eudowood Sanatorium and was there three months. Patient then moved to the country and a letter of October 2, 1912, states that he is feeling better than he has felt

for a long time; has no cough, appetite is good and he has gained in weight.

No. 5239, W. Z., white male, aged 41 years, came to the dispensary on December 21, 1909, complaining of cough. He dated his illness from April, 1909, when he had pneumonia and was confined to bed for four weeks. Had had cough ever since then.

Patient was a fairly well nourished man, but very pale and of sallow complexion. There was marked involvement of both sides, with a large cavity in the left upper lobe.

The 1 per cent conjunctival and the cutaneous tests were positive. Tubercle bacilli were found in the sputum.

Patient entered Eudowood Sanatorium in the spring of 1910. A letter from his wife dated August 15, 1912, says that patient is now living in the country on a small farm and is strong enough to work it himself. He still has some cough and expectoration, but his general condition is good, and he has gained somewhat in weight.

As a parting glance at Table I, we invite inspection of the columns headed "well" and "deaths from tuberculosis." The gradual increase in the proportionate number of deaths in the different groups is striking. The figures suggest how futile are our efforts to treat successfully poor patients with pulmonary tuberculosis, advanced beyond the incipient stage.

TABLE II.—THE AFTER HISTORY OF PATIENTS IN RELATION TO THE TUBERCULIN TESTS.

		Became tuberculous.	Did not become tuberculous.
Not tuberculous.	Reacted to 1% conjunctival test.	4-10	1-100
	Reacted to 5% conjunctival test.	0-0	5-100
	Reacted to the cutaneous test....	1-3	31-97
	Negative to conjunctival test....	4-3,8	100-96
Doubtful.	Negative to cutaneous test.....	1-18	75-98
	Reacted to 1% conjunctival test.	4-7	31-83
	Reacted to 5% conjunctival test.	7-7	41-13
	Reacted to the cutaneous test....	5-7	25-98
Probable.	Negative to conjunctival test....	7-7	68-95
	Negative to cutaneous test.....	7-7	77-94
	Reacted to 1% conjunctival test.	11-39	5-31
	Reacted to 5% conjunctival test.	5-26	14-74
	Reacted to the cutaneous test....	17-16	20-54
	Negative to conjunctival test....	2-17	10-83
	Negative to cutaneous test.....	1-10	9-99

Table II is arranged to show the relation of the tuberculin tests in patients becoming and those not subsequently becoming tuberculous. As our previous results have shown the 1 per cent conjunctival test is an important indication of active tuberculous disease and therefore, we look with most interest to the results derived from it. It will be seen that in the non-tuberculous group the four cases that later became tuberculous failed to react to the 1 per cent conjunctival test; whereas, the one case that did react has remained well. In the doubtful group of the 16 cases that subsequently became tuberculous only four originally showed a reaction to the 1 per cent conjunctival test. As far as the small number of cases collected can show anything, they indicate clearly that proportionately, the same number became tuberculous of those who reacted and of those who did not react to the tuberculin tests. We are therefore justified in concluding tentatively that the tuberculin tests are of value only in reference to the condition of the patient at the time they are given. Such a high grade of tuberculin hypersensitiveness as is indicated by a reaction to the 1 per cent conjunctival test is not to be used as



evidence of the presence of tuberculous disease when other clinical evidence is absent. A reaction to the 1 per cent conjunctival test, taken as an isolated fact, does not cast a gloomy shadow over the subsequent years of the reactor's life.

In the probable group, it will be noted, 69 per cent of those reacting to the 1 per cent conjunctival test became tuberculous, whereas but 23 per cent (the 5 per cent positive and the negative conjunctival cases combined) of those negative to the 1 per cent test became tuberculous. We have insisted that the patients in the probable group are really tuberculous and therefore these figures are further proof of the diagnostic value of the 1 per cent conjunctival test.

TABLE III.—THE AFTER HISTORY OF TUBERCULOUS PATIENTS IN RELATION TO THE TUBERCULIN TESTS.

		Well.	Advancing.	Dead.
Incipient.	Reacted to 1% conjunctival test.....	7—58%	1—8%	4—33%
	Negative to 1% conjunctival test.....	1—6%	2—14	0—0
	Reacted to cutaneous test.....	9—64	2—14	3—21
	Negative to cutaneous test.....	4—37	2—28	1—14
Moderately advanced.	Reacted to 1% conjunctival test.....	6—19	7—21	19—60
	Negative to 1% conjunctival test.....	0—0	3—20	3—20
	Reacted to cutaneous test.....	15—35	10—23	18—42
	Negative to cutaneous test.....	0	0	4—100
Far advanced.	Reacted to 1% conjunctival test.....	9—9	6—6	85—85
	Negative to 1% conjunctival test.....	2—4	4—8	43—88
	Reacted to cutaneous test.....	11—9	6—5	101—85
	Negative to cutaneous test.....	0	4—13	27—87

We have arranged Tables III and IV to give an answer to the question of the prognostic value of the tuberculin tests. In the incipient group, 33 per cent of those who reacted to the 1 per cent conjunctival test have died, while the six who failed to react are still living. In the moderately advanced group, a larger proportion have died of those reacting than of those failing to react to the 1 per cent conjunctival test. In the far advanced group the proportion between the two classes is practically the same.

TABLE IV.—COMPARISON OF LENGTH OF LIFE AND RESULT OF TUBERCULIN TESTS IN PATIENTS DYING OF PULMONARY TUBERCULOSIS.

		Death within 6 mos.	Death within 6 mos. to 1 yr.	Death within 1 yr. to 2 yrs.	Death over 2 yrs.
1% conjunctival test.	Positive..	38—34%	34—30%	26—23%	14—12%
	Negative..	23—43	14—26	6—11	11—20
5% conjunctival test.	Positive..	8—42	7—37	1—5	3—16
	Negative..	11—44	2—8	4—16	8—32
Cutaneous test.	Positive..	50—34	47—32	28—19	21—14
	Negative..	11—58	1—5	3—16	4—21

Table IV indicates that in patients dying of tuberculosis, the length of life following the administration of the tuberculin tests is approximately the same in those who react as in those who do not react to the tuberculin tests.

We cannot discuss in detail the relation of tuberculin hypersensitiveness to tuberculous disease. We wish merely to call attention to the view that tuberculin hypersensitiveness is a measure of resistance to tuberculous disease. Certain important experiments upon animals have been interpreted as supporting the view and many prominent students of tuberculosis

have subscribed to it. They hold that a tuberculous patient with a high grade of tuberculin hypersensitiveness offers a better prospect of recovery than one with mild or absent hypersensitiveness. Further, they regard attempts to diminish hypersensitiveness by tuberculin treatment as ill-advised. We have not shared these views. Our work with tuberculin in diagnosis and treatment has led us to believe that tuberculin hypersensitiveness in relation to tuberculous disease runs, roughly, somewhat as follows. Since nearly all adults are infected with tuberculosis, we assume a low grade of tuberculin hypersensitiveness to begin with. Should there be a fresh invasion of the body from within or from without, the tuberculin hypersensitiveness rapidly rises. If the disease subsides and the individual recovers the hypersensitiveness gradually falls to a lower level, perhaps to the original low level; if the disease remains active, the high level of hypersensitiveness persists and lasts until the body is overwhelmed and its resistance broken down completely by the disease when hypersensitiveness disappears. Therefore, while we allow that in rapidly advancing cases, the absence of tuberculin hypersensitiveness is an ominous sign, in early and moderately advanced cases, we consider a low grade of hypersensitiveness a more favorable indication than a high. The high level hypersensitiveness rebellious to tuberculin treatment we have found to be of particularly unfavorable prognostic import.

TABLE V.—RESULTS OF THE REPETITION OF THE CUTANEOUS AND CONJUNCTIVAL TESTS.

		Repeated in			
		Less than 1 yr.		1 to 2 yrs.	
		Pos.	Neg.	Pos.	Neg.
1% conjunctival test.	Pos.....	1		1	2
	Neg.....			5	12
5% conjunctival test.	Pos.....				2
	Neg.....	1		3	9
Cutaneous test.	Pos.....			3	1
	Neg.....			2	1
					16
					12
					18
					19

Table V is arranged to show the results of the repetition of the conjunctival and cutaneous tests. As is well known, the application of tuberculin occasions a local stimulation of hypersensitiveness. A conjunctival test negative to one instillation may become violently positive if the instillation be repeated after a few weeks' interval. Our object was to see how long this local excitation persists. Of 50 patients negative to the 1 per cent conjunctival test, 12 were positive to a second instillation repeated from one to three years later. However, of these 12 cases four had in the interval become definitely tuberculous and five presented symptoms and signs pointing strongly to the presence of an active tuberculous lesion. Only three of the cases had remained unchanged in their general and local condition. It would appear, therefore, that the sensitiveness occasioned by a conjunctival instillation of tuberculin in most instances completely disappears within two years; in some individuals it may persist for two years and longer.

# THE INFLUENCE OF THE CONTENTS OF THE PULMONARY ARTERY ON EXPERIMENTAL PULMONARY TUBERCULOSIS.

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WITH

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There are certain broad biological problems associated with pulmonary tuberculosis of the animal organism which have received surprisingly little attention in experimental laboratory work; yet these problems seem to me so fraught with importance that for two years our laboratory has devoted its whole time to their study.

So much of the investigation in tuberculosis during the past few years has been directed towards establishing a relation between this infection and the results of immunological studies in other infections, and especially the studies in anaphylaxis, that we have in a measure lost sight of some of the significant features of the disease that require elucidation before we have a foundation on which to build.

At the outset of this paper it may be well to state some of the unexplained anatomical facts which are evident to experimenters; to follow this with a review of some of the more prominent physiological processes connected with these conditions, and in conclusion to outline the methods of procedure attempted by us to clear away the difficulties; and finally to state the results of the work accomplished up to the present time.

In pulmonary tuberculosis in man and cattle there is undoubtedly a point of attack which is fairly constant. In man this is at the apex of the upper lobes; in cattle at the apical region of the caudal lobes. I think it may safely be said that this varying point of attack in the two animals is in some way connected with the posture of the animal, and probably with the fact that when the animal is on its feet the vessel which supplies the area usually infected in each case arises from the highest level of the blood stream. This fact opens the way for the constant operation of the law of gravity on the substances which form the component parts of the blood at the point of origin of these vessels from the parent stream.

If we examine the subject from this standpoint, it is pertinent to inquire first what substances are contributed to the blood stream in this region in such a way as to exert a possible influence by gravity or otherwise on a pulmonary infection.

It will be seen at a glance that the lung tissue gets first pick at a very striking contribution from various sources that no other organ in the body can boast:

1. The contents of the thoracic duct.
2. The contents of the hepatic veins.
3. The contents of the renal and suprarenal veins.

The substances contained in these vessels arrive from their

various fields of production at the portals of the right side of the heart to receive a final churning here before being poured into the comparatively slow stream of the pulmonary artery, and from here spread out over the broad bed of the lung capillary system.

In calling special attention to these contributions to the blood stream, it is not intended to indicate that the contents of the blood from more distant regions have no bearing on this problem, but the above substances bear the stamp of grosser individuality and consequently have been chosen for the earlier studies.

The contents of these channels of contribution to the right heart require a more detailed account:

1. Through the thoracic duct there come chiefly large quantities of neutral fat in fine globules and granules, as well as cholesterin and lecithin, resulting from the action of bile, gastric, pancreatic, and intestinal secretions on the fats of the food.
2. Through the hepatic veins there come the blood sugar changed from glycogen by the action of diastase, the fats mobilized from the subcutaneous tissues and altered by the action of the liver and pancreatic secretions.
3. Through the renal veins the secretions of the kidneys and suprarenal bodies.

To arrive if possible at the influence of these various contributions to the pulmonary stream on tuberculosis infection in the lung, we outlined the following scheme of study:

## THE INFLUENCE OF THE CONTENTS OF THE THORACIC DUCT.

1. Of various fats on the growth of the tubercle bacillus in vitro and on the tubercle bacillus in the lung.
  - (a) Glycerin and higher alcohols.
  - (b) Fatty acids and soaps.
3. Of bile on the tubercle bacillus—
  - (a) Before entrance to the lung.
  - (b) Mixed with fats on the tubercle bacillus in the lung.
4. Of various salts, such as—
  - (a) Phosphates.
  - (b) Calcium.
5. Of various solutions which precipitate salts, such as—
  - (a) Sodium citrate for calcium.

\* Read at a meeting of The Laennec, a Society for the Study of Tuberculosis, The Johns Hopkins Hospital, March 31, 1913.

## THE INFLUENCE OF THE CONTENTS OF THE HEPATIC VEINS.

1. Of liver altered animal fats—
  - (a) On the growth of the tubercle bacillus in vitro.
  - (b) On the tubercle bacillus growing in the lung.
2. Of liver and pancreatic secretion altered fat in vitro.
3. Of glucose—
 

Hypoglycemia	{	By glucose injection.
	{	By adrenalin injection.
	{	By pituitary extract injection.
	{	By thyroid extract injection.
Hypoglycemia	{	By injection of hydrazin.
4. Of surgical interference by—
  - (a) Artificial stenosis of hepatic and pancreatic veins.
5. Of interference with liver function—
  - (a) Phosphorus poisoning.
  - (b) Starvation.

## THE INFLUENCE OF RENAL AND SUPRARENAL SECRETIONS ON EXPERIMENTAL PULMONARY TUBERCULOSIS.

1. By the injection of renal extract intravenously.
2. By the injection of suprarenal extract intravenously.
3. By interference with kidney function by—
  - (a) Phloridzin.
  - (b) Other irritants.
4. By artificial stenosis of renal and suprarenal veins.

## THE INFLUENCE OF VARIOUS DRUGS DIRECTLY APPLIED TO THE PULMONARY STREAM.

- Fat solvents—ether, chloroform, benzol—
- (a) By inhalation.
  - (b) Ether and chloroform intravenously.

It will be readily seen that such a scheme of study involves many years of work, and only parts of it have been accomplished up to the present time. In presenting what has been done I ask your tolerance of its incompleteness and the lack of positive conclusions which I am able to offer.

In the animal experiments in this series of observations, we have confined ourselves to rabbits and guinea-pigs. Rabbits are mostly used because of the ease of reaching the pulmonary stream through the ear vein.

We have used both bovine and human tubercle bacilli chiefly from the strains Bi and H<sub>37</sub>, obtained from Saranac Lake through Dr. Baldwin.

## EXPERIMENTAL PULMONARY INFECTION WITH TUBERCLE BACILLI.

Tubercle bacilli introduced into the animal body by various routes produce widely different distribution and grades of infection.

Subcutaneous injection produces a generalized tuberculosis, in which the liver usually escapes infection.

Intraperitoneal injection produces the most widespread generalized tuberculosis of all organs.

Gastro-intestinal introduction of tubercle bacilli is the most varying of all routes in its resulting infection. This route varies greatly with the animal used. Nearly all animals require very large doses to produce infection in this way. Especially is this true of guinea-pigs, which are so susceptible to the other routes of injection. Young pigs and monkeys are much more susceptible to this mode of infection. The resulting infection by this route is usually a glandular one, but may be pulmonary and generalized, depending largely on the dose.

By intravenous injection through the ear vein in rabbits, however, we are able to procure a more or less pure pulmonary infection with a varying slop-over infection of the kidneys and spleen.

## LUNG CHEMISTRY.

I cannot do more than refer in this paper to certain striking phenomena of lung chemistry, such as the large lipase content and the specific character of the lung capillary endothelial cells and their affinity for tubercle bacilli, but these points must eventually be carefully studied and correlated with other results before the final conclusions of this infection are reached.

## THE VIRULENCE AND DOSE OF THE TUBERCLE BACILLUS.

Such important factors as the virulence of the tubercle bacillus; the resistance of the animal to the dose of the bacilli; the disappearance of the tubercle bacilli from the blood stream; and similar factors have also a very striking bearing on this whole problem and cloud the experimental field more often than is generally appreciated. On no other grounds can I explain the varying results obtained in certain experiments carried out in one litter (the progeny of but two adults), in which individuals were found to yield strikingly different results to the same treatment.

In carrying out this work we have not forgotten the structure of the tubercle and its lack of blood supply, but we have thought that the chemical constitution of the region of tuberculous development in the lung as determined by its blood supply might have some fundamental bearing on the choice of a site by the tubercle bacillus.

I will now describe the results of our various experiments without wearying you with too great an amount of detail:

## TEST TUBE EXPERIMENTS.

We found that various fats added to plain glycerin agar in the test tube had varying influence on the growth of the tubercle bacillus. Some fats markedly increased the growth; others prevented any growth.

The fats used in these experiments were—human fat, rabbit fat, beef fat, olive oil, palm oil, linseed oil, and cod liver oil. The fats were chosen largely on the basis of their content of the several fatty acid radicals—stearic, palmitic, oleic, linoleic, and linolic acids. They were examined for their influence on both bovine and human strains of tubercle bacillus.



Human fat, butter, and olive oil always stimulated the growth of the human bacillus.

Beef fat, olive oil, and linseed oil stimulated the growth of the bovine bacillus.

The other fats had a restraining influence on the growth of the organisms.

When extract of liver (dog, rabbit, and guinea-pig liver), prepared to conserve the lipase (Kastle), was added to the fats and incubated for two to three hours before adding them to the agar in the test tubes, all of the digested fats, except cod liver oil, stimulated the growth of both types of tubercle bacillus when compared with the growth on plain glycerin agar.

When the tubercle bacilli from these various fat tubes were injected into the ear veins of rabbits and into the peritoneal cavity of guinea-pigs in doses of 1 mgm., they were invariably more virulent than the tubercle bacillus grown on plain glycerin agar.

This was also true of the tubercle bacilli grown on the liver altered fat tubes.

In a series of similar experiments in which tubercle bacilli was grown on beef, rabbit, and butter fats, treated with dog liver extract plus dog spleen extract, the organisms were more virulent when tested on rabbits in the above way, but those grown on olive oil and cod liver oil were less virulent.

#### INFLUENCE OF VARIOUS OILS ADDED TO THE PULMONARY STREAM.

Series of rabbits were injected with 1 mgm. of bovine tubercle bacilli, grown on egg media, and treated by injecting various crude fats into the ear vein daily, every second day, and every third day, following the infecting dose.

The fats used were the same as in the test tube experiments—human fat, beef fat, olive oil, palm oil, cod liver oil, and linseed oil. The average dose of the fat was .25 cc.

The resulting infection in the rabbits treated in this way was always more severe than in the untreated rabbits. This was especially marked in those rabbits treated with olive oil, which we used in more experiments than the other fats on account of its fluidity.

In the olive oil treated rabbits, we found at times large cavities produced, which we have never found in hundreds of injections of untreated rabbits.

#### LUNGS STORED WITH VARIOUS FATS.

We found that by injecting various fats into the ear vein that the lungs retained a large quantity of fat, producing in them a tough, oily consistency, with soapy feel and appearance. We consequently administered in several series of rabbits successive doses of the above fats, giving as high as seventeen doses of .25 cc. olive oil; seven doses of .25 cc. linseed oil, fresh unsalted butter, human fat and beef fat; and followed this with 1 mgm. of bovine tubercle bacilli. In all of these animals the resulting infection was much more severe than in the untreated rabbits. Rabbits vary greatly in

the amount of fat that can be administered in this way—some animals died in convulsions with severe pulmonary congestion after the second and third doses. Others took as many as seventeen successive doses without symptoms of any sort.

#### INJECTIONS OF GLYCERIN.

On the basis of the theory that fat taken in the food is broken up in the intestine into glycerin and fatty acids, we next tried the influence on pulmonary tuberculosis of adding glycerin in frequent doses to the pulmonary stream. We have not yet used any of the higher alcohols.

Glycerin is well known to be one of the valuable adjuncts in stimulating the growth of the tubercle bacilli on artificial media. As one of the essential components of fat, we tried the influence of glycerin on the development of tuberculosis in the lung by adding this alcohol to the pulmonary blood stream through the ear vein of rabbits.

Several series of rabbits, each series of one litter were injected with .5 mgm. of bovine tubercle bacillus through the ear vein. Commencing on the next day following the bacillary injection, all but one of these rabbits were treated by ear vein injections of .5 cc. of 25 per cent glycerin, one receiving 36 daily injections; one 20 similar injections every second day; and one 16 injections every third day. At the end of 40 days these animals were killed and compared with the untreated control.

In all of these experiments the treated animals lost weight more rapidly, and had much more extensive tuberculosis, the tuberculous processes being larger and more degenerated than in the untreated animals.

Similar series were injected with 3 mgm. of human tubercle bacillus and similarly treated. In these the glycerin injections had the same effect, the treated animals having more tuberculosis in size and number of the tubercles than the control animals.

#### SOAPS OF FATTY ACIDS AND FATTY ACIDS.

In these experiments we have used only sodium oleate and oleic acid. Only the soap was tried on the pulmonary infection. In three series of rabbits which received .25 cc. of 1/10,000 solution of the soap, the treated rabbits all lost weight more rapidly than the controls, and had more severe and larger tuberculous lesions.

Oleic acid, besides its irritant action at the site of the injection, produced a very curious, soapy translucent condition in the lung, which we have not studied further.

#### INFLUENCE OF BILE.

These experiments are still in progress. The indications, however, seem to be, from two series of animal experiments and many smears of tubercle bacilli mixed with rabbit bile and incubated for one to 24 hours, that the tubercle bacilli clumps are broken up, the resulting lesions more scattered, and the organisms less virulent.

Our impression from these experiments has been that we may find here an explanation of the difficulty of producing infection through the gastro-intestinal tract in most animals, and of the absence of pulmonary infection in man from the large numbers of bovine bacilli which he seems doomed to drink with his milk.

We have not yet touched the experiments on the influence of bile and pancreatic juice on fats in their relation to pulmonary infection; the experiments involving surgical interference; nor the influence of salts.

#### CALCIUM PRECIPITATION BY SODIUM CITRATE SOLUTION.

Sodium citrate solution has the property of precipitating free calcium. With the idea of finding out if such a solution added to the pulmonary blood stream would aid the precipitation of calcium around tuberculous deposit on the possibility of free calcium joining the same stream through the thoracic duct, in conjunction with Dr. Lester Hollander, we injected rabbits with experimental pulmonary tuberculosis with increasing doses of sodium citrate solution from 1 mgm. up to 256 mgm. In rabbits living over two months there was extensive fibrosis with marked deposit of lime salts around the lesions both in the lungs and in the kidney.

In a series in which we injected sodium citrate solution and calcium lactate solution in opposite ear veins at the same time, the rabbits died immediately in convulsions.

#### INFLUENCE OF HEPATIC VEIN CONTENTS.

The experiments with liver altered fats have been confined to test tube experiments and have been referred to earlier in this paper.

#### HYPERGLYCEMIA.

The question of the influence of sugar on tuberculous infection of the animal body has long since held a conspicuous place as a clinical observation. So far as I know, the subject has not been made the object of experimental investigation from our standpoint. Nor has the question of relation of the two conditions, hyperglycemia and tuberculosis, kept pace with the rapid progress of our knowledge of diabetes. Recently Montgomery has made a careful analysis of the subject from a statistical and clinical standpoint, but in such studies the pathogenesis of the diabetes has not been taken into account, and it is evident that not all diabetic conditions have an equal relation to the tuberculosis process.

In approaching this subject we have had in mind the various forms of experimental diabetes, dependent on the chromaffin system; the pancreas; the ductless glands; the alimentary system; phloridzin; and Brown-Séquard's puncture, or the nervous system. On only three of these can we report at the present time:

1. On hyperglycemia caused by the injection of suprarenal extract, and thus producing an excessive sugar output on the part of the liver.

2. On hyperglycemia caused by adding glucose directly to the blood stream.

3. On diabetes caused by phloridzin, which does not carry with it a hyperglycemia, but probably causes its diabetes by its action on the kidney cells.

The pulmonary tuberculosis was produced in the ordinary way, by the injection of bovine tubercle bacilli into the ear vein of rabbits.

In several series of rabbits with pulmonary tuberculosis, treated with 1 cc. of 1/10,000 solution of suprarenal extract intraperitoneally and subcutaneously every second day for two months, the results were variable, but when there was any influence, it reduced the resulting infection.

One very interesting issue of this work was the different result on the kidneys and heart by subcutaneous and intraperitoneal injections.

After long continuous subcutaneous injections, the kidneys are astonishingly increased in volume—often to double the normal size.

After long continued intraperitoneal injections, the kidneys remain normal in size, but the heart becomes tremendously hypertrophied—to double the normal size in one instance.

Hyperglycemia from subcutaneous injections of glucose always increased the severity of the tuberculous infection.

Phloridzin diabetes apparently had no influence on the pulmonary infection.

By exclusion, it seems likely that if any of the hyperglycemias have a marked influence in increasing the severity of tuberculous infection, it is probably those due to the pancreatic system and the thyroid gland. This seems more likely from a clinical standpoint from the frequent enlargement of the thyroid gland accompanying tuberculosis infections.

#### PHOSPHORUS POISONING.

In using phosphorus poisoning to eliminate the influence of the liver on the content of the pulmonary stream, we are dealing with a complex alteration of metabolism. The general conclusions on the results of phosphorus poisoning in animals may be summed up as follows: The total metabolism is decreased; protein metabolism is increased; carbohydrate metabolism is probably increased; while fat metabolism is probably markedly decreased, leading to a decreased amount of fat and fat split products in the blood. In addition to this the alkalinity of the blood is diminished.

It will thus be seen that if phosphorus poisoning has any influence on experimental pulmonary tuberculosis, a process of eradication of the various component parts of such a condition would be necessary before any conclusions could be drawn.

We have so far studied the change in two series of rabbits.

In the first series of five rabbits, four were given pulmonary tuberculosis in the usual way—two of these were poisoned by phosphorus, receiving 1/25 grain daily for 4 days, and then 1/50 grain daily for eight days. They were killed at the end of 14 days and compared with one control. In the phosphor-

ized animals, which became emaciated very rapidly, the tuberculous processes were less than in the control.

The fifth rabbit was poisoned with phosphorus, 1/25 grain daily for four days before the injection of 1 mgm. of bovine tubercle bacilli, and after the dose of bacilli received 1/50 grain of phosphorus daily for 12 days. This was killed 19 days after infection and compared with rabbit No. 4, *i. e.*, the second control which had its infecting dose of tubercle bacilli four weeks before. This phosphorized animal also had less marked tuberculous processes than the untreated animal.

The second series consisted of four rabbits—all were given 1 mgm. of bovine tubercle bacilli through the ear vein; and three were phosphorized with 1/50 grain twice daily for four days, then once daily for four days, and were killed at the end of three weeks.

In the three phosphorized animals in this series, also, the tuberculous processes were less severe in size and number than in the untreated animal.

The phosphorus was administered by mouth in pill form; the livers of all animals were large, yellow, and fatty; the kidneys were yellow, soft and flabby.

The tubercles in all the phosphorized animals had a striking yellow tinge.

Any explanation of these results without further study would be useless, but the results may have something to do with a diminished amount of split fat products in the pulmonary stream.

#### STARVATION.

We have studied only one series of guinea-pigs so far to find the influence of starvation as a whole on the tuberculous process. This was entirely unsuccessful. Six pigs were given 3 mgm. of bovine tubercle bacilli by mouth, and three starved for four days, and then fed lightly for three weeks. The controls were given full diet. All the animals, save one of the unstarved, failed to develop tuberculosis, and this one had only a bronchial gland infection of mild degree.

#### RENAL VEIN INFLUENCE.

We cannot yet offer any data on this phase of the subject, save that given in the hyperglycemia studies above.

#### INFLUENCE OF FAT SOLVENTS BY INHALATION.

We have conducted experiments on many series of animals to find, if possible, if any of the ordinary fat solvents could be administered in such a way as to influence pulmonary tuberculous lesions.

#### ETHER AND CHLOROFORM.

These experiments have been conducted in several ways:

1. The lungs were saturated with ether and chloroform by inhalation for thirty minutes, and immediately following this,

while the animals were still asleep, were given 0.1 mgm. of tubercle bacilli in the ear vein. They were allowed to live 44 days, when they were killed and compared with the controls. In the treated animals the tubercles in the lungs were less in number and much smaller than in the control, but the treated animals had more spleen and kidney lesions.

2. In several series, rabbits with pulmonary tuberculosis, produced by 0.1 or 1 mgm. of bovine tubercle bacilli, were etherized by inhalation with 15 to 25 cc. of ether daily for 20 to 30 minutes for as long as two months and ten days. We could not determine that such treatment had any constant influence on the pulmonary lesions when the animals so treated were compared with untreated controls. We were struck with the frequency with which we could etherize these animals without apparent influence on their general health. We could find neither glycosuria nor albuminuria in the etherized animals. If, however, they were exposed to cold air during the winter too soon after etherization, they frequently died of general pulmonary congestion.

#### BENZOL.

Animals with pulmonary tuberculosis (1 mgm.) allowed to inhale 2 cc. of benzol, under a glass cover, daily, every second day, and every third day, all showed less tuberculosis in size and number of tubercles than the untreated controls.

From these experiments, it is possible that ether and chloroform inhaled immediately before infection in rabbits may have some influence in reducing the amount of tuberculosis produced by tubercle bacilli introduced in the ear vein; that ether inhaled daily, or less frequently, for many days after such tuberculous infection has no influence on the pulmonary lesions; and that inhalation of benzol may have some restraining influence on the pulmonary lesion when administered after this has been produced.

I am sorry that this work is not nearer completion; also that the microscopic study of the gross experiments has not been touched up to the present time. When we have had time to complete it, we will, I hope, have something more to offer.

In recounting the nature and results of our experiments, we have refrained from explanation, preferring to confine ourselves at the present time to the facts only. I feel, however, that it is fair to conclude:

1. There is some close relation between the content of the fats and split fat substances in the pulmonary stream and the severity of experimental pulmonary tuberculous lesions.

2. That increasing the percentage of carbohydrate content of the pulmonary stream by the influence of extracts of the suprarenal gland, has no influence on experimental pulmonary tuberculosis.

3. That the inhalation of such fat solvents as ether, continued over long periods of time, has no direct influence on experimental pulmonary tuberculosis.



# THE PHYSICIAN'S OPPORTUNITY IN PREVENTIVE MEDICINE.\*

By JOHN B. HAWES, 2d, M. D., Boston, Mass.

Prevention is to-day the watchword of medicine. At the present time no physician who attempts merely to cure disease and not to prevent it can be said to be doing his duty toward the community. In tuberculosis as in all other conditions new methods of treatment are constantly being discovered. A few prove of great and lasting service; the majority do not. In the meantime, often without pay, usually without adequate pay or reward there are many physicians engaged in preventive work which will eventually place tuberculosis and other similar diseases under our control. I refer to the physicians occupying public positions whose aim it is to prevent disease rather than to cure it. They are the family physicians not of sick individuals, but of sick communities. In this paper I shall describe what these men are doing in my own state, what they have done and what they hope to do, the handicaps under which they work, and the rewards, financial and otherwise, which they receive. I shall try to give a clear picture of the difficulties and disappointments which one meets with in this work, as well as to present the other side, the vast opportunity open to men, and particularly young men, trained in one of the best, I will not say the best, medical schools in the world to be of service to city, state and country.

My own position in Massachusetts is a particularly advantageous one from which to view the field, in that I am not only a health officer in the employ of the state, but also a general practitioner in the city of Boston, especially interested in tuberculosis. It was far from my original plan to go into state work. I had fully expected to enter the field of general medicine and through my good fortune in becoming the assistant of Dr. F. C. Shattuck I had every reason to continue along the smooth roadway of the private practitioner. In 1907, the late Dr. Arthur T. Cabot, newly appointed chairman of the State Tuberculosis Commission, asked me to act as secretary to the board. As this position not only drew a salary which seemed to me large but also permitted of my continuing my work with Dr. Shattuck, my own private practice, such as it was, and my work at the Massachusetts General Hospital, I gladly accepted Dr. Cabot's offer. This position with constantly increasing duties and responsibilities I have held ever since.

At first I felt very strongly that many of my medical friends, particularly the older ones, not only for my own sake thoroughly disapproved of my taking up any state work, however minor a position it might be, but also that they looked askance at those who left the straight and narrow path of surgery, internal medicine or the laboratory bench. Doubtless many of these physicians would vigorously deny that they ever felt in this way. Every public health officer, however, who, during the last ten years has been actively at work, will

agree with me that this feeling was not an uncommon one. During the past two or three years, in Massachusetts at least, there has come a very remarkable change in the attitude of the medical profession toward the doctor in public office. The development of preventive medicine has brought this about. Doctors are coming to realize that while in their general practice or limited specialty they may cure this or that individual patient, disease as a whole, and the mass of the people as a whole, cannot be reached in this way. They have come to respect and not to look down upon the men who are in public service. The public is realizing that protection from tuberculosis, typhoid fever and infantile paralysis does not come from the private practitioner, no matter how great his skill, but that it depends on municipal and state efforts wisely directed by physicians trained and devoting their lives to this work.

I crave your indulgence for what I have said concerning my own start in this field. My excuse is that I believe my experience has been an instructive but not uncommon one; that it represents a condition of affairs now relegated to the past and that the attitude of the medical profession to-day toward the physician in public service is in happy contrast to what it was even only six years ago. With this introduction I shall now consider, in as practical a manner as possible, the various positions open to physicians in which they can be of service to the community in which they live. Conditions in Massachusetts to a greater or less extent find their counterpart in other states.

Such positions naturally divide themselves into two classes, those that are paid and those that are unpaid. The former list includes town and city physicians, school and factory inspectors, positions on local boards of health, officers of state boards of health and other state boards, superintendents or assistant superintendents and physicians in state or local tuberculosis sanatoria, hospitals and other institutions, and finally, positions in the state legislature. Unpaid positions include the officers of state and county medical societies, positions of trust in local anti-tuberculosis associations, members of unpaid boards of trustees of local or state institutions, members of unpaid state commissions and members of local or state boards of health.

*Town or City Physicians.*—In smaller cities, and in practically all towns, there is always some position which corresponds to what in Massachusetts is called the city physician. Too often this office is under political control and is handed out as a reward of merit. The physician can usually carry on private practice of his own, and can do the city work at his own convenience. His work is under the supervision of the local board of health; it consists in caring for indigent cases either in their homes or in institutions, and especially in investigating contagious cases reported to the board. The salary runs from \$500 to \$2000. Whether this position is or

\* Read at a meeting of The Laennec, a Society for the Study of Tuberculosis, The Johns Hopkins Hospital, February 24, 1913.

is not held in respect and esteem by the medical profession and by the public at large depends upon the caliber of the incumbent. I know of several physicians holding such positions, who I am sure are doing splendid work, especially in tuberculosis; I also know of others who are not. The position is an honorable one and one in which a high-grade man could be of immense benefit to his community.

*City Bacteriologists.*—The salary of a city bacteriologist runs from \$500 to \$2000 depending on the amount of time given to the work. Except in the cases of large cities where this is a department of the board of health and where there may be a number of physicians giving their whole time to the work, a city bacteriologist can carry on his own private practice giving one to four hours a day to the laboratory.

*Milk Inspection, Etc.*—There are often other minor paid positions, such as inspectors of milk, water supply, etc., under local boards of health. Too often they are under political influence and rarely occupied by high grade men. The salaries are small.

*Local Boards of Health.*—A local board of health may be an admirable institution or it may be a school for turning out cheap politicians. Too often, in Massachusetts at least, local boards seem to be of the latter type. In many of the smaller towns there is no medical man on the local board, or, indeed, there may be no health board of any kind, the selectmen acting as such. As a general rule, the best physicians have no opportunity and make no attempt to secure positions on such boards, nor does the public yet demand that the medical profession have adequate representation on them. The tenure of office is only a temporary one and the salaries are not large, \$100 in smaller towns, to \$1000 in cities; they are large enough to attract non-medical office hunters but not enough to secure the services of the best physicians. Local boards of health, however, are slowly improving. The time is not far distant when a strong public opinion will not tolerate political influences in the administration of its health affairs. Opportunities for young men, fairly good now, are bound to become better. There is no greater opportunity than this for the highly trained young physician, not only to raise the standard of health work in his community to a height never before dreamed of, but also to gain for himself name and fame, which will bring their own reward.

*School Inspection.*—There is hardly any subject in medicine concerning which more is being written and more accomplished than school hygiene. Proper school inspection is a necessary and integral part of such school hygiene. Until comparatively recently in smaller cities or towns, either there was no school inspection or else it was done in a purely perfunctory way, the most important part of the physician's duty being to draw his salary. This is rarely the case at present. The public fully realizes the value of fresh air rooms, open air schools, and that it is better to keep the child well than to wait until he gets sick before placing him under proper conditions at home and at school. The standard demanded in this work is constantly rising; unfortunately, the salaries have not yet risen in proportion. In the city of Boston there

are 87 school inspectors, civil service appointees, under the supervision of Dr. W. J. Gallivan, chief of the division of child hygiene. These physicians are paid \$500 to \$1000 a year and are required to give two hours daily to the children under their care. There is also a large corps of school nurses working in conjunction with these doctors. While the present system is by no means a perfect one, it is immensely superior to anything in this line Boston has heretofore enjoyed. It is the desire of the chief of this department, and indeed of all those interested in the subject, that the amount of time required of each physician and the salary paid him be steadily raised. In smaller cities and towns the salary of the school physician is much less and his duties much less clearly defined; as a general thing, the quality of the work is proportionately low. It rests solely with the individual physician whether such school inspection be purely perfunctory or whether it really amounts to something. One school inspector, a busy man in general practice, in addition to his stated duties, has arranged for a series of short health talks to be given by specialists to the high school pupils under his care. These talks include such subjects as hygiene, tuberculosis and its prevention, the care of the teeth, etc. I spoke to such an audience of over 1000 bright and intelligent pupils the other day and was glad of the opportunity to do so. This kind of "school inspection" is preventive medicine on a large scale. This position, wherever it may be, is one of great and growing importance; the physician who undertakes this work, regardless of inadequate remuneration, and who does it conscientiously and intelligently, will soon gain an enviable place for himself in his community wherever that may be.

*Welfare Work in Factories, Workshops, Department Stores and Large Corporations.*—There is a steadily growing feeling among manufacturers and other large employers of labor that from the financial point of view alone it is more profitable to keep their employees well than to allow them to get sick and try to care for them after they become sick. The really progressive employers try to do both. They are learning that healthful conditions are an asset in their business. This necessitates the help of doctors and nurses. Such positions as these are admirable ones for younger physicians. Not only is the salary usually paid a good one, \$1000 to \$1500 or over, while in addition the range of medical and surgical cases is wide and varied, but also such a position often gives the physician holding it his first practical example of the meaning of the words "preventive medicine." I have been through the workshops and addressed the employees of the Dennison Manufacturing Company, which admirable concern employs a physician and a nurse, each of the highest standing, to look after the welfare of the men and women in the factory. Never have I seen more hygienic workrooms nor a healthier and more contented group of employees. Such positions as the one here described are rapidly increasing in number. A man undertaking this work will at once find opportunities to prevent disease and to become a factor in the health of his community, which he probably would not have met until after many years of general practice and perhaps never.

*State Health Work. State Board of Health.*—In Massachusetts the position of secretary and the assistant to the secretary of the State Board of Health command good salaries and are at present occupied by physicians of high standing, who give all of their time to the work. Massachusetts has so far been fortunate in that these important positions have been kept out of politics, and in consequence are sought after by men of good training and ability. Those who hold these positions are, in general, looked up to and respected by the medical profession and the community at large. The salaries are from \$3000 to \$5000.

*State Inspectors of Health.*—The position of state inspector of health is a comparatively new one in this state and in many other states does not exist at all. Our health inspectors are appointed by the governor each year; they are not yet under civil service. The salary paid varies from \$1200 to \$2500 per year depending on the size and population of the individual district. The state is divided off into fourteen health districts. Among his other duties the health inspector in charge of a given district, acting under the supervision of the State Board, is supposed to see that laws in regard to factory and workshop hygiene are enforced, to carry out investigations of epidemics or of special diseases as directed by the State Board, and to advise local boards of health and direct their work when necessary. One most important duty of health inspectors is to examine into the health of all minors employed in factories, and to inspect the sanitation of factories, workshops and tenement houses where clothing is made. One inspector in one year examined as a part of his work the sanitary conditions of 342 factories of 63 different industries employing 31,000 hands, of whom 3,800 were minors. Another inspector has made a special study of a number of trades in which workers are exposed to dusts, to irritating and poisonous fumes, to extreme degrees of temperature and humidity. The industries so far studied include the textile industry, the pearl industry, felt hat industry, mattress and curled hair industry, the rubber industry, the making of jewelry, metal polishing and buffing, and a group of industries in which workers are exposed to lead poisoning. Although it was understood at the beginning that this work need not interfere with nor prevent the carrying on of general practice by the physicians accepting these appointments there is no doubt but that it has seriously interfered with the practice of many of the inspectors and that in many ways they have to curtail their private work. This at best is unsatisfactory. The work is large enough to demand the full time and energy of a highly trained physician; the salary should be large enough to permit of this. However, this may be, these positions offer splendid opportunities for the highest kind of service. At present there is no adequate financial reward; in the future, and I believe in the near future, the public will see the value and need of this work and will demand that these positions be multiplied and the salaries increased.

There are numerous other salaried positions under any well organized state board of health. These are usually full time appointments and do not allow of private practice. Among

such positions one might name those of bacteriologists, inspectors of cold storage plants, physicians engaged in making special investigations, etc.

*Secretaryships of State Commissions.*—My own position is an example of this type. The work I do fits in excellently with that of my private practice and each helps and augments the scope of the other. Such work throws one into contact with problems of all kinds, and doctors and patients of every description, and most important of all gives one a clear perspective of the big administrative side of preventive medicine, which can rarely be gained from private practice. The salaries usually paid in such positions which permit of private practice vary from \$1500 to \$2500.

*Superintendents and Resident Physicians of State, Municipal or Private Tuberculosis Sanatoria, Hospitals or Other Institutions.*—In Massachusetts, as elsewhere in the east at least, there is a dearth of good men who are willing to take up institutional work. The reasons for this are plain. The deadly routine, comparative isolation, and on the whole low scale of salaries are sufficient to lead most men to prefer to take their chances at private practice. This is the state of affairs at present. I do not believe that it will last long. Public opinion will demand that men of the highest and best type be obtained for these positions and that such men need make no sacrifice, as many of them now do, to take up this form of medicine. In our state sanatoria the superintendent receives \$2500 salary and a comfortable home for himself and his family; assistant superintendents get from \$900, the lowest, up to \$1800, the highest, with, but more often without, accommodations for wife and family. Personally I believe that these salaries should be raised 25 to 50 per cent; in a few years I feel sure that they will be so raised. But even as they are, these positions offer opportunities for young men to support themselves and get the best of training along certain lines during their earlier years of practice, as well as opportunities to do yeoman's service in preventive medicine. What I have said here in regard to our tuberculosis sanatoria applies equally well to the many other similar positions in hospitals for acute or chronic diseases or in institutions for the criminal or the insane.

*Positions in the Legislature.* In Massachusetts, as well as in other states, there are always a few physicians in the Senate or House of Representatives. Occasionally the doctors holding such offices are of the highest type; as a general rule, in Massachusetts at least, they are good average men; not infrequently they are purely politicians. I believe that in Massachusetts such physicians at the State House are conscientious and sincere in their desire to do good. They are, however, usually untrained for such work; they rarely have had any previous opportunity to look at medicine from a broad, administrative point of view; they are not forceful in debate or public speaking and their influence for good is apt to be lost in the maelstrom of political give and take. Again, they are rarely helped as they should be, or backed up by the state medical society which is only too apt to take no active part in legislative affairs. The opportunity to do much good in this



direction is ever present. I could not advise any physician to enter the field, however, unless he was fully trained to this work, willing and able to devote to it not one year but many years, and unhampered by the thought of a neglected private practice.

*Other Salaried Positions.*—There are many other salaried positions the details of which I will not go into but will merely enumerate. Various state boards such as the Board of Charity, or its equivalent, the Board of Insanity, state water boards and civil service and industrial commissions, offer positions drawing good salaries to physicians trained along certain lines. Various philanthropic societies such as those connected with baby hygiene, mental hygiene, milk bureaus, tuberculosis, eugenics, vital statistics, etc., employ physicians, most of whom are able to carry on private practice in addition.

In the preceding pages I have gone over the chief salaried positions open to physicians, particularly the younger men. I shall now consider what I call the higher positions, whose chief reward, in addition to some increase of reputation of uncertain value, is the feeling that one is helping to accomplish good work and to bring about real progress.

*Local Anti-Tuberculosis Societies.*—Beginning with the smaller local positions, I would at first call attention to those connected with local anti-tuberculosis societies. During the last ten years in Massachusetts, I have seen the number of such local societies increase and multiply until now every city and every large town has an organization of some kind doing anti-tuberculosis work. No one can really estimate the amount of good these societies have done. I can, however, name off a long list of local day camps, municipal and private tuberculosis hospitals and sanatoria, out door schools, dispensaries and district nursing associations, whose existence has been brought about entirely by the influence of these local societies. But, back of the local societies, I can also name a long list of men, young doctors and old doctors, and all busy doctors, each one dependent on his practice for his living, who have given freely of their time, influence, wisdom and energy to bring about what I have described. To you, in Baltimore, the names of J. F. A. Adams of Pittsfield, Bowers of Clinton, Getchell of Worcester, Alfred Worcester of Waltham, and many others, may possibly mean but little; to us in Massachusetts they mean men who have stepped out of the rut of private practice, often to the detriment of their private practice, to be real leaders in the fight to prevent disease. To them the state owes a debt it can never adequately pay.

*County Medical Societies.*—The chairmanships of county medical societies are few in number and usually bestowed as a reward of merit. Too often the man holding such a position regards it in exactly this way and does not exert himself to make what should be made of it. The chairman should do more than simply preside, but most of them do not. He can be a great influence for good in his medical community by leading in new movements, formulating plans, and by helping to direct public opinion providing he has courage and inclination to do this.

*Boards of Trustees of State or Local Institutions. State Commissions.*—Massachusetts still holds to the system of managing most of the state institutions by means of unpaid boards of trustees; many of the biggest pieces of preliminary survey work which have led the way to the establishment of new hospitals and sanatoria, or to the enactment of beneficent legislation, have been done by such unpaid boards and commissions. Such work is arduous; it takes much time; it often meets with the severest and most unjust criticism. The men carrying it on are known as such and such a board, and rarely as individuals. It takes real public spirit and real patriotism for the busy physician striving his best to earn his living and often having hard work to do it, to accept such a position and give it the necessary time, energy and thought. His only reward will be the increased esteem of those members of the medical profession, the value of whose good opinion cannot be measured in dollars and cents.

*Training in Preventive Medicine.*—Up to the present time men occupying any of the positions, paid or unpaid, which I have enumerated above, have had practically no special training to fit them for the work they were called upon to do. The reason for this was that there was no opportunity for such training. A physician accepting a public service position usually entered upon his work with absolutely no previous experience of any kind; he felt his way along, making many and sometimes serious blunders; but, if wise and conscientious, profited by them until he became an able and competent health officer.

This state of affairs no longer exists. The medical profession and the public alike demand that the men in charge of health matters must be highly trained and specialists in their work. At the Harvard Medical School, and at other schools, there is a department of preventive medicine which is constantly growing in its influence and scope. This department, under the charge of Dr. Milton J. Rosenau, offers the degree of Doctor of Public Health to those completing the course. The demand for physicians who have taken this course and received this degree of D. P. H. is constantly increasing and will soon exceed the supply. I am assured that during the past six months at the Harvard Medical School, there have been more than six requests for men well trained in public health work, at salaries varying from \$2400 to \$7000 a year. In addition to this, the department is now about to offer another and shorter course open to graduates, which will provide a splendid opportunity for physicians about to take up some form of health work, who cannot spare the time necessary to acquire the full degree of Doctor of Public Health. This new course, in addition to other things, will include actual field work under the supervision of the State Board of Health and other agencies.

It is evident, then, that in the not far distant future the doctor who intends to take up preventive medicine must regard it as a specialty and a most exacting one, requiring special study and training. Success in this branch, as in other branches of medicine, can only come by devoting one's entire time to the work, and not only time but heart and

soul. Ten years from now it will be difficult to combine private practice with public health work. The general feeling of the community is gradually reaching the point where it sees that the training of the ordinary doctor does not fit him to be a sanitarian. There is no excuse, even at the present time, for any medical student not securing the best possible training for public health positions.

Meanwhile, until the time arrives when adequate salaries are paid to public health officers, so that no financial sacrifice need be made by those entering this field, many physicians will have to combine private practice with whatever public office they may hold. Except in the larger cities it may be many years before this millennium arrives. That it is coming there can be no doubt. The next generation of doctors will find a condition of affairs in this regard far different from what now exists. This, however, does not lessen the responsibility of the doctors of to-day, and especially the younger doctors, toward preventive medicine. The conditions which I have described above are not peculiar to Massachusetts. They exist everywhere. It is far easier to stick to private practice or to develop some specialty, than to endure the criticism and disappointment often met with even in the humblest of public positions. But nowhere in private practice can be found such opportunities to prevent disease and to be of real service to the community as are ever present in each of the positions above described.

There are two men, familiar to you all, whose names will be handed down in the history of Massachusetts and of preventive medicine in this country. The first is Dr. Henry P. Walcott, chairman of the Massachusetts State Board of Health, who, without remuneration, for over a quarter of a century has been the acknowledged leader in the fight to protect the health of Massachusetts citizens and to eradicate disease from their midst. I need not mention his further service to the state through his connection with Harvard University and the Massachusetts General Hospital. Criticism, disappointment, even slander and abuse, have never let him swerve from his lofty aims. He has been a true physician to the state.

The other name that I would mention is that of Dr. Arthur Tracy Cabot, who died November 4, 1912. Six years ago Governor Guild appointed Dr. Cabot member of an unpaid state commission given wide powers to direct and control the tuberculosis campaign in this state. Dr. Cabot was at once elected chairman of this board, which position he held up to the time of his death. Despite the fact that he was a surgeon of national reputation, an acknowledged leader in his specialty, and had a large and lucrative private practice, he accepted this position and the duties and responsibilities which went with it. Shortly after this, he gave up his practice and devoted all of his time and energy to the service of the state. The future alone will show the true worth of these services; even at present, however, his influence is plainly evident. I know of no finer monument than that which has been erected to Dr. Cabot. When he took hold of the tuberculosis work in this state, there was little of order and system, and much of

chaos in our methods. The state was in urgent need of a master mind and firm guiding hand to direct and lead the scattered forces. Such a mind and guiding hand Dr. Cabot gave at immense personal sacrifice. He has directed the building of three new state sanatoria; he has seen local hospitals for advanced consumptives increase and the death rate from this disease diminish; he has been influential in placing school and factory hygiene upon a proper basis; he has united the medical profession and developed among the public a deep-rooted conviction that tuberculosis can and must be eradicated.

We cannot all hope to accomplish as much as these two men have done, but, at least, we can do our share. I have tried in the limited scope of this paper to point out in a practical way the opportunities for such work as this. As I have shown, rarely is the financial reward adequate to the time and labor expended; but there are many things more worth while than rewards in dollars and cents. There is a sense of satisfaction that is well worth having in feeling that one is playing a part, however minor a part, in work which aims not only at the good of the individual but of the community. In addition to this, if I read the signs of the times aright, this is to be the medicine of the future. It seems to me, then that it is our very urgent duty, not only as physicians but also as citizens, to be ready and willing to do our share, to step aside from the routine of private practice and to take part in this world-wide effort not only to cure but to prevent disease.

### ARMY MEDICAL CORPS EXAMINATIONS.

The Surgeon General of the Army announces that preliminary examinations for appointment of First Lieutenants in the Army Medical Corps will be held on July 14, 1913, at points to be hereafter designated.

Full information concerning these examinations can be procured upon application to the "Surgeon General, U. S. Army, Washington, D. C." The essential requirements to secure an invitation are that the applicant shall be a citizen of the United States, shall be between 22 and 30 years of age, a graduate of a medical school legally authorized to confer the degree of Doctor of Medicine, shall be of good moral character and habits, and shall have had at least one year's hospital training as an interne, after graduation. The examinations will be held simultaneously throughout the country at points where boards can be convened. Due consideration will be given to localities from which applications are received, in order to lessen the travelling expenses of applicants as much as possible.

In order to perfect all necessary arrangements for the examination, applications must be completed and in possession of the Adjutant General at least three weeks before the date of examination. Early attention is therefore enjoined upon all intending applicants. There are at present forty vacancies in the Medical Corps of the Army.

### NEW PUBLICATIONS.

The following three monographs:

**Free Thrombi and Ball-Thrombi in the Heart.** By J. H. HEWITT, M. D. Price, \$1.00.

**Benzol as a Leucotoxin.** By LAURENCE SELLING, M. D. Price, \$1.00.

**Primary Carcinoma of the Liver.** By M. C. WINTERNITZ, M. D. Price, 75 cents.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore. Other monographs will appear from time to time.

## NOTES ON NEW BOOKS.

*The International Medical Annual. A Year Book of Treatment and Practitioners' Index.* Thirty-first year. \$3.50. (New York: E. B. Treat & Company, 1913.)

Carefully prepared as it is by leading English and American specialists, this Annual is an excellent review of the progress of medicine during the past year. No such work can satisfy all demands, but for the general practitioner it is a most useful volume. Some reviews do not seem to be up to date—*ex.*, the diseases of the pituitary body, where there is no reference to Cushing's work, and the writer appears not to know that the gland has been operated upon successfully in a number of patients. The volume is well illustrated, is of convenient size and neatly printed.

*Handbook of Diseases of the Rectum.* By LOUIS J. HIRSCHMAN, M.D. Second Edition Revised and Rewritten. (St. Louis: C. V. Mosby Company, 1913.)

This book appears as a second edition and has been revised and rewritten. The chief improvements made have been in the illustrations of the book, and in the attention devoted to local anesthesia. The illustrations are particularly good and constitute perhaps the most valuable feature of the entire work, including four colored plates and numerous prints from radiographs. Besides the body of the book which Hirschman himself has written there are incorporated two chapters by other authors. Dr. John L. Jelks of Memphis, Tenn., has written the chapter on dysentery and Dr. George W. Wagner of Detroit, is the author of a chapter on the examination of the feces. As a whole the book strikes one as being unoriginal, and not particularly needed.

The volume is expressly designed to serve the general practitioner, and hence contains no description of the larger operative procedures in this field of work. There is, however, extensive consideration of the operations which may be done under local anesthesia, and this feature of the book is its best claim to being worth while. The general arrangement and contents of this volume differ in no important way from the numerous other books on the same subject, and except that the material is perhaps more readable and condensed the reviewer finds no special worthiness in the volume now under consideration.

*Lang's German-English Dictionary of Terms Used in Medicine and the Allied Sciences.* Second Edition Edited and Revised by MILTON K. MEYERS, M.D. \$5. (Philadelphia: P. Blakiston's Son & Co., 1913.)

There are but few medical students who read German with ease, and this well printed dictionary will be a real boon to them. It is not too large to be readily and frequently turned to, and with its nearly 50,000 words will very seldom fail to give the

reader what he wants. It would be an incalculable help to the profession if there were similar dictionaries in other foreign languages, as good as this one.

*Appendicitis—Its Diagnosis and Treatment.* By JOHN B. DEAYER, M.D., etc. Fourth Edition Thoroughly Revised. \$4. (Philadelphia: P. Blakiston's Son & Co.)

Appendicitis, both acute and chronic, is one of the commonest affections the surgeon meets with, and he could have no better book than this on which to found his surgical procedure. This last edition shows many changes since the third appeared. The excellence of Dr. Deaver's work has been recognized long since, so that this volume needs no new word of appreciation, except to mark it as the most authoritative work on the subject in English.

*Organic and Functional Nervous Diseases.* A Text-book of Neurology. By M. Allen Stan, M.D., etc. Fourth Edition, Thoroughly Revised. Illustrated. (New York and Philadelphia: Lea & Febiger, 1913.)

The many excellencies of this text-book have been known for years to neurologists and general practitioners, and it is fortunate for the profession that Dr. Stan has found time to prepare this new edition, which contains all that is essential in the newer studies of neurological diseases, that has appeared since the preceding edition. It is a work in every sense well adapted to the needs of medical students, and one which holds a foremost rank among American books of medicine.

*Principles of Hygiene, a Practical Manual for Students, Physicians and Health Officers.* By D. H. BERGEY, M.D., Fourth Edition. Illustrated. \$3. (Philadelphia and London: W. B. Saunders & Co., 1912.)

We have already had the opportunity of commenting favorably upon previous editions of Bergey's text-book of hygiene, and take pleasure in referring to the fourth edition which has recently appeared. This edition is considerably larger than previous ones, and includes many of the most important advances which have been made in hygiene during the past few years. The section on quarantine is particularly good, giving in detail the quarantine laws in the United States in regard to shipping from foreign countries, and those governing interstate commerce. It is unfortunate that the author has not given in greater detail the various methods which are employed in hygiene especially since most students employ a book of this character as a guide to laboratory work. The book is full of information, however, is written in simple English, is essentially readable and can be heartily recommended.

## BOOKS RECEIVED.

*American Association for Study and Prevention of Infant Mortality.* Transactions of the Third Annual Meeting, Cleveland, Ohio, 1912. 8vo. 383 pages. 1913. The Franklin Printing Co., Baltimore.

*Bovine Tuberculosis and Its Control.* By Veranus Alva Moore, B.S., M.D., V.M.D. Thirty full page illustrations. 1913. 8vo. 134 pages. Carpenter & Company, Ithaca, N. Y.

*Annual Report of the Surgeon General of the Public Health Service of the United States.* For the fiscal year, 1912. 1913. 8vo. 261 pages. Government Printing Office, Washington.

*Year-Book of the Royal Society of London.* 1913. 8vo. 258 pages. Harrison and Sons, London.

*Eighth Biennial Report of the Board of Control of State Institutions of Iowa.* For the Biennial Period ending June 30, 1912. 1912. 8vo. 736 pages. Emory H. English, Des Moines.

*International Clinics.* A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by Henry W. Cattell, A.M., M.D. Volume I. Twenty-third Series. 1913. 8vo. 302 pages. J. B. Lippincott Company, Philadelphia and London.



- Systematic Case-Taking. A Practical Guide to the Examination and Recording of Medical Cases.* By Henry Lawrence McKisack, M.D., M.R.C.P., Lond. 1913. 12mo. 166 pages. Paul B. Hoeber, New York.
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# BULLETIN

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### SURGICAL JUDGMENT.\*

By J. M. T. FINNEY, M. D.,

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"Life is short, art is long, experience fallacious, judgment difficult." With the pregnant aphorisms of the illustrious Father of Medicine, every member of this Society is doubtless quite familiar. Fruitful with suggestion, they, along with other of his writings which have come down to us, merit frequent reading, and will richly repay careful study. Even in this twentieth century of advanced knowledge and boasted scientific achievement, a close acquaintanceship with them will stimulate thought and action to higher purpose and to greater endeavor. Indeed, in view of the indifferent character of much of the work that is still being done, of many of the doctrines that are still being taught, of much of the literature with which the medical press teems (to use a mixed metaphor), "half baked" and crude as much of it is, and yet, nevertheless, often stated in terms of Delphic cock sureness—in view of all this, let me repeat, it would appear that the sage aphorisms of the

great Hippocrates that have to do with the fallaciousness of experience and the difficulty of judgment, acquire a new significance and apply to our day and generation with peculiar force and meaning.

It has seemed to the writer, therefore, when reviewing the various topics appropriate for consideration in an address such as this, that it might be worth while upon this occasion to depart somewhat from the conventional, and to attempt to analyze, imperfectly though he may, wherein, more especially in the domain of surgery, lies the great difficulty in the way of the attainment of sound and correct judgment, and in what consists the fallacy of experience.

This is a difficult task which we have set ourselves, because it will be at once apparent that judgment and experience are very closely associated and interdependent the one upon the other, and that in the consideration of each one separately, and in their several relations one with the other, there are many different factors to be borne in mind, the relative measure of importance of which, it will be found impossible accurately to determine.

\* Presidential address read before The Southern Surgical and Gynecological Association, December 18, 1912, Old Point Comfort, Va.

So far as experience is concerned, it will be readily admitted that the fallacy to which Hippocrates has reference must, from the nature of the case, be inherent. It lies in the improper interpretation of certain phenomena which, from time to time, have come under observation. Furthermore, there is also the liability to error in the correctness of the observations themselves, and, not only this, but there is additional opportunity for error in the fact that these experiences, which must of necessity be recurrent in character (obviously they cannot all happen at once), must be recorded either in the mind of the observer or upon paper, or by other mechanical device, for temporary or permanent record. To err is human! It would seem, therefore, unnecessary to repeat what must be apparent to all, namely, that the possibility of error, common to everyone of these phases, is very real, nay, more than this; owing to the imperfection of our sense perceptions, of all of our mental faculties, of our so-called instruments of precision, of our records, there must be somewhere the absolute certainty of error. It is simply a question then as to how relatively great that error will be, and not as to whether or not it will exist at all. Since then, as we have seen, experience is founded upon repeated observations of certain phenomena, and observation of these various phenomena is made through the senses, and record must in some way or other be made of these observations for subsequent reference, and then by processes of the mind, they must be rightly interpreted in order to form the bases of correct judgment, it can readily be seen that in this interchange, abundant opportunity for error will be afforded.

Let us pursue this line of reasoning a little further. Since these various stages, through which experience must necessarily pass before it can express itself in terms of definite action, are so prone to error, and since in so many important decisions experience is looked to for guidance, and since it so largely influences our judgment and actions in the domain of surgery, as it does in all other affairs of life, and since it often, quite unconsciously perhaps, plays such an important rôle in controlling and directing our impulses, it would appear to be of the utmost importance to consider this problem from a practical standpoint, and to point out, if possible, some way in which improvement along these lines can be made, and our accumulated experiences, an extremely valuable asset when properly interpreted and utilized, rendered less liable to error. This is the purpose of this address. The writer, even if he were able to do so intelligently, has no desire to invade the domain of psychology, or to launch into a discussion of abstruse philosophical subjects which may possibly be suggested by the topic chosen, but which would be distinctly out of place upon an occasion such as this.

The practical question suggested by this discussion which concerns every one of us, and not only us, but our patients as well, is this, "Is there any way in which this liability to error can be materially reduced, and our experiences, vast and varied as they are, rendered a safer guide to our judgment?" Fortunately for all concerned, to this query an affirmative answer can be given. Many, indeed all, of the processes involved, are capable of development and improvement. In other words,

we are at once confronted with the problem of education, medical education, in some of its manifold forms, and when I use the term "medical education," I do not use it in any restricted sense. I do not have in mind simply the four years that are ordinarily spent in the medical school, and the year or two in the hospital, for are we not, all of us, at any rate those who will, learning all the time, being educated continually, led out, as the word implies, into larger fields, with an ever-widening horizon; with attractive vistas opening up here and there, beckoning us on and inviting us to enter into other spheres of greater opportunity and usefulness?

It is not our intention, however, to discuss the general question of medical education, further than to indicate, if possible, certain ways in which it may have a distinct bearing upon the subject under discussion. To do more than this would be foreign to our purpose and would lead us too far afield.

It will be readily admitted, I believe, that the physician above all others, is the man whose education should be broad and complete, for to him are entrusted the lives of his fellowmen, and inexperienced physicians, young or old, without adequate preliminary and professional training, should not be permitted to practise so serious a profession. Unfortunately, however, for one reason or another, such permission is granted far too easily at the present time. The fault lies partly with the public in not only permitting but, to a certain extent, encouraging the ignoramus and the charlatan. It would go a long way toward the eradication of this evil if the public would exercise more care and discrimination in the selection of medical men, especially surgeons. The true, well qualified physician, and the self-styled doctor do not and ought not to look alike. But the blame for this deplorable condition of affairs lies chiefly with the profession itself, for it is a lamentable fact that medical education and ideals in this country are low, lower, perhaps, than in other civilized countries. The reason for this is because our medical colleges are, on the whole, so far below the standard set by the rest of the civilized world that it shames us to make a comparison. These facts have been known long and deplored bitterly by the more enlightened members of the profession, but the investigations of the American Medical Association covering a period of several years, and the exhaustive work of Mr. Abraham Flexner of the Carnegie Foundation recently published, no longer leaves the public any valid excuse for their ignorance or of apathy toward the prevailing conditions. As a result of the effect produced by this report, a considerable number of low-grade medical colleges throughout the country have been compelled to close their doors. In this connection let me quote from the late Dr. M. H. Richardson, an honored Fellow of this Society, a man who was himself the personification of the best type of surgeon, and who represented the highest ideals in the profession; he says, "The task before me is a serious criticism of what is going on in every community. There is to my mind no doubt whatever that surgery is being practised by those who are incompetent to practise, by those whose education is imperfect, who lack natural aptitude, whose environment is such that they never can gain that personal experience which



alone will really fit them for what surgery means to-day. They are unable to make correct deductions from histories, to predict probable events, to perform operations skilfully, or to manage after treatment."

What a scathing criticism of our beloved profession, and the especial sting in it lies in the fact that it is unfortunately only too true! Let us for a moment consider this question, for it is fundamental to the production of sound judgment, and let it be understood that what is here said is said in no "I am holier than thou" spirit, for every honest man knows that he makes mistakes, both of judgment and execution, and the writer is no exception to this rule.

From the very nature of the case, surgery must be considered as a specialty and the attributes of specialism are insight, knowledge and experience, and their proper application to practice is impossible without thorough comprehension and mastery. This can only be properly done by one who has been trained from his youth up, and who has been thoroughly well grounded in the fundamentals of the science. Unless one knows and thoroughly appreciates the principles concerned in the handling of tissues, in the repair of wounds, in the causes and results of inflammation, in the characteristics and manner of growth of malignant disease, in the principles of physical science involved in the production and reduction of fractures and dislocations, and in a hundred other points of importance, which time would fail us to mention, he cannot ever hope to get a thorough grasp of questions which are vital to the complete understanding and proper management of surgical problems of every-day occurrence.

It has been said that a surgeon, like a poet, is born and not made. Personally, I do not believe that this statement is altogether true. Unquestionably, some individuals are born with a natural aptitude for surgery, a something which has been characterized as the "surgical instinct," and which every teacher can recognize at once as present in varying degrees in the medical students under his care. It is very far from the writer's purpose to belittle in any way the art of surgery which is of very great importance, and which in the hands of some skilled operators certainly has become developed to the highest degree. It must be conceded, nevertheless, that however high a pinnacle the art may occupy, the science of surgery always will overshadow it, and unless one is well grounded in the principles of true scientific surgery, it must degenerate into something of a trade or a sort of slight-of-hand performance.

My honored preceptor, the late Dr. John Homans, of Boston, a man of wide experience and excellent judgment, and possessing in an unusual degree the characteristics and knowledge which we have been endeavoring to describe, remarked upon one occasion, "Any fool can cut off a leg; it takes a surgeon to save one." This very well illustrates the point that I am endeavoring to make. Surgery is not alone an art. There is a wide distinction between operator and surgeon. The day of the barber surgeon is over. "It is a science, founded upon certain fundamental principles, without a thorough knowledge and understanding of which, no man can do his patient or himself justice."

Now what is the application of all this? If our premises are correct, the conclusion is obvious, namely, that no doctor, no matter who, without a thorough surgical training, has the moral right to attempt to make a practice of surgery. He may succeed in doing certain minor operations or even certain major operations well; he may learn to do, mechanically, certain things fairly satisfactorily to his patient and to himself, and he may have a fair percentage of success; but, sooner or later, he will meet his limitations, and in attempting to go beyond these, with his small and imperfect equipment, some of the catastrophes of surgery will happen, and then who pays the price of his ignorance and temerity? Yes, let me repeat, surgery is far too serious a matter to be lightly undertaken by those who are not thoroughly trained in the fundamental principles underlying its proper performance. Right here let me sound a note of warning, and in so doing I do not wish to be misunderstood—the tendency nowadays is toward the multiplication of hospitals, a tendency that is to be encouraged under proper safeguards. With the general proposition that a hospital is the only place in which to be sick, that is, surgically sick, I am in the heartiest accord, provided only that the hospital is under proper management, and that the surgeon, for I am speaking now only of the surgical aspects of the question, is thoroughly competent to handle surgical cases. But what do we see? As a matter of fact, in my own state, and I think that it probably is a correct index of the situation throughout the country, hospitals are multiplying in many of the smaller towns, towns of a few thousand inhabitants, where there are few or no skilled surgeons, and—here is the danger—where the general practitioner, against his better judgment, is tempted to essay the rôle of surgeon. There are two general reasons for this, aside from the undesirability of performing any operation in a private house. In the first place, the responsibility for a surgical operation in a private house is undivided. The surgeon alone is responsible for the good or bad results, whereas in a hospital it is somewhat different. The cause of this is not easily explained, but it is true nevertheless, that in the case of a patient operated upon in a hospital, there is not the same feeling of individual responsibility upon the part of the surgeon held by the community at large, as in the first instance. In the second place, under the cover of the hospital, and in the more or less seclusion of its operating-room, the would-be surgeon is tempted to do things that he would not dare to do under other circumstances. Particularly is this true, and this is no joke, where the operating-room is furnished with all the modern appliances of the up-to-date hospital. I have in mind now a certain beautiful operating-room in a hospital in a small city, a room walled and ceiled with marble, finished with polished brass and shining glass, everything in it of the costliest description. What is the result? It would appear to the uninitiated impossible, in such an hygienic sanctuary, to commit a surgical sin; and yet one constantly sees in that operating-room heinous crimes committed against the most fundamental surgical principles and technique, which ought always to be kept inviolate. And why is this? Because of those who habitually use this room, not one is a trained surgeon; they have, so to speak, just picked it up.

In the gradual evolution of this palpably wrong condition of affairs, the surgeon himself, or more strictly speaking, some surgeons, are not wholly blameless. There is no royal road to surgery. There is no such thing as surgery made easy. There is no trick about it that can be learned in a ten lesson course by watching the manual dexterity of some especially clever operator, and hearing him vociferously declaim against the old accepted principles of the fathers, and the newer scientific or so-called laboratory methods. It is easy to be led by such false gods into believing that anybody can perform a surgical operation, it looks so easy and it seems so simple, as they do it. But do not be misled into the fatal error of supposing that that is all that there is to it. It means a long, hard journey, years of close application and study, of mental and manual training, of observation and investigation in hospital ward and laboratory, before a man can acquire the experience, the insight, the judgment in sufficient degree, to entitle him to the proud distinction of being rightly called a surgeon, and all that it implies. Says Valentine Mott, than whom I know of no one better qualified to judge, "We regard those as surgeons and those alone who have by conscientious devotion to the study of our Science, and the daily habitual discharge of its multifarious duties, acquired that knowledge which renders the mind of the practitioner serene, his judgment sound and hands skilful, while it holds out to the patient rational hope of amended health and prolonged life." (Quoted by Barnesby.)

The remedy for all this is obvious, do not abolish hospitals but restrict the practice of surgery to the trained surgeon. There would then be no further excuse for such books as that which has recently appeared by Barnesby entitled, "Medical Chaos and Crime," much of the contents of which is unfortunately only too true.

There is also a moral side to this question. The inexperienced operator, owing to lack of proper training and insufficient experience, is often necessarily at fault, both as to his judgment and execution. He is attempting to do something that, in the vast majority of cases, he is not competent to do for the reasons above mentioned. He is placing himself in a false position before the community, and is laying himself open to charges, which in the present enlightened condition of the public, and certainly in some parts of the country, it would be difficult for him to disprove. There are those in every community who, stimulated by shyster lawyers of the ambulance-chasing type, are not slow to take advantage of every mistake, or fancied mistake, upon the part of the operator. It is well, therefore, for every doctor, no matter who, before he essays the part of surgeon, to weigh well the responsibilities that are involved. He should be in a position to prove to an intelligent jury that he has given his patient the benefit of skill equal at least to that which can reasonably be expected from the average well-trained surgeon. This, it appears to me, it would be difficult, indeed impossible for the untried operator to do. The thoroughly conscientious man will think twice and and go very slowly before allowing himself to be forced through an error in judgment into this position. Of course, I am not now referring to those cases of emergency surgery which every physician at

times is called upon to perform. In these instances, common humanity and surgical instinct demand that the best be done for the patient and that immediately, even to the extent of a capital surgical operation, in order to relieve his suffering, or to save life, pending the arrival of the skilled surgeon. Then, too, this matter of operating by those not prepared for it, tends toward the lowering of moral and ethical standards in other directions. It is a great temptation to do this sometimes, because the vast majority of doctors are dependent for their living upon the returns from their practice, and it frequently means a great deal for a doctor to turn over to the surgeon a good patient, perhaps wealthy and prominent in the community, in which event the surgeon, after the operation, collects a substantial fee, while the doctor too often receives little or no recognition or pecuniary return for his advice and services.

The cure for all this is to come by enforcing the highest standards in medical ethics and in medical education, and it is to be hoped, an added hospital year as a prerequisite to practice.

It is our duty, yours and mine, to see that medical education is limited to those institutions that can and do give proper opportunities to their faculties and students, and who have sufficient backbone to hold both strictly to account. We should also strive to get public sentiment aroused in support of this necessary advance. The signs of the times are fortunately most encouraging, a widespread and intelligent interest is being taken in educational problems. Particularly is this true of medical education, with a resulting increase in moral and material support. Encouraging too is the growing number of medical schools that are fighting, against tremendous odds, to modernize their equipment and methods of instruction, to foster research and idealism, and to turn out only such graduates as any one of us might welcome in case of sickness, and to whom we can cheerfully intrust the future maintenance of the highest medical standards and the progress of medical science and practice.

The point which we have been endeavoring to make clear, and it is the basis of our whole argument, is that education, broad, long-continued, careful, conscientious, comprehensive, thorough, is the foundation of all good, sound surgical judgment, and that without this previous training, there is in truth no such thing.

Says President Hibben, "Our general knowledge serves to illumine the specific portion of it, which is the special object under contemplation."

The close relationship existing between experience and judgment has already been referred to. His accumulated experiences are of value to the surgeon only in so far as they are correctly interpreted. They may become a source of positive harm if they are improperly understood or applied. Indeed the larger the experience that one has had that has been misunderstood or improperly interpreted, the more dangerous does that surgeon become, for his judgment will eventually be so vitiated and warped thereby, that in his mind right may become wrong, and wrong right. This condition of affairs may be observed in almost every phase of life, in politics, in law, in

medicine, even in theology, for what is Christian Science, that bastard offspring of an unholy union between pseudo-science and false religion, what is it, but a false interpretation of certain phenomena, the existence of which is well recognized? It has been well said of it that "What is true in it is not new, and what is new in it is not true." What of the various "isms" with which the history of medicine is punctuated? What of certain political dogmas that have from time to time held temporary sway in our own and in other lands? All founded upon false theories, the result of a misconception, an improper interpretation of facts, real or imaginary. Are our own individual experiences always accurately observed and recorded? Are they properly interpreted? And when transformed into action, mental or physical, are they always wisely governed by judgment, ripe, sound, born of accurate observation, correct record, proper interpretation, sane reasoning? Are they?

Shakespeare whose wonderfully accurate observation entitles him to be heard upon almost any subject, has this to say: "Experience is by industry achieved, and perfected by the swift course of time." How very true! The same idea is in a measure conveyed by the adjective most often employed in describing the individual whose experience is such as to entitle him to be heard, and his judgment to a measure of respect above that of his fellows, namely, "ripe." The surgeon who by his industry in seeking out additional opportunities for observation along all lines pertaining to his profession, by his painstaking accuracy, by his time-consuming thoroughness, by his careful attention to irksome routine and detail, both in examination and record of his cases, and by burning the midnight oil in the study of the recorded experiences of others, and in mature reflection upon those of his own, has at last, his judgment mellowed like ripened fruit, become "perfected by the swift course of time." He it is who has in truth "by industry achieved" experience and a sound judgment.

"In the investigation of any subject concerning which we regard ourselves entitled to a judgment, not only should we seek as wide a range of observation as is possible concerning the facts upon which we found the judgment, but we should acquaint ourselves also with what other men have thought and written upon the subject. This is to be done not that we may slavishly acquiesce in their judgment, but that by a critical examination of all that is known and reported, we may be the better able to defend our own position, or the more reasonably to modify or to abandon it, as the case may be" (Hibben).

What is it that constitutes good surgical judgment? Is it something that is born in a man and not made? Is it a thing that one man has without working for, without trying especially hard to get, and which another cannot acquire, no matter how hard he may try? When present as one sees it now and then in certain individuals developed to a marked degree, how does it manifest itself? Can it always be recognized and defined when present, or is it a quality that can better be understood than described?

Before proceeding to define this particular process of the mind, let us try to analyze it a bit and consider some of its

more important characteristics, also some of the aids that may be made use of in its acquisition, as well as some of the more common errors in the way of formulating correct judgment. To begin with then, one of the most important characteristics of judgment may be defined as insight. "By this term, one means some kind of knowledge, but the word has a certain peculiar significance whereby we distinguish what we call insight from knowledge in general. A man knows the names and faces of his acquaintances, but he has some sort of insight into the character of his familiar friends. A physician knows the way to his office where he sees his patients, but if he is a successful doctor, in the highest sense of the term, he has insight into the structure and functions of the human body in health, the nature and laws governing disease, its various manifestations, its causes, methods of prevention and cure. He must have an intimate knowledge of human nature in its varying moods and phases, he must know something of therapeutics and the action of drugs. He must know something of the fundamental sciences of chemistry, physics, bacteriology, biology, physiology and psychology, etc. He must know something of the indications for and the methods of use of the various instruments of precision used in his calling. In short, insight is a name for a special sort and degree of knowledge, that unites a certain breadth of range, a certain intimate acquaintanceship, a certain sureness of grasp, whereby one is brought into near touch with the objects of his insight. It gives us a view of some connected whole of things, of cause and effect. We can only truly gain this insight when our acquaintance with our object is coherent, close and personal. It can never be obtained at second hand; many things can be learned by rote and hearsay, but if you have won insight into your profession, you have won it not without the aid of your own individual experience" (Royce). Yet experience, characterized by Hippocrates as fallacious, and admitted by common consent to be such, is not of itself sufficient to produce insight, unless the coherence, the breadth of range, the ability to properly correlate and interpret are also present. This insight is not always confined to the scholar or to the learned, but may belong to the unlearned as well. Many otherwise, ignorant and unskilled people have won a great deal of insight into the matter that intimately concerns them. Many very erudite and learned people possess little or no practical insight into anything. Why is this? Simply because accurate observation, the proper association of cause and effect, the ability to discriminate between the important and the unimportant, in short, the knowledge that has been gained is in the former case coherent and personal, while in the latter it is vague and impersonal, and cannot therefore, serve any practical purpose. It goes without saying that honesty is fundamental to the production of good judgment. This fact is at once recognized by the laity as well as by the profession. If the slightest suspicion rests upon an individual as to his entire good faith, how quickly and how hopelessly is his opinion upon any matter discredited. How can anyone reach a proper conclusion who has been dishonest in his premises? How easy it is to fall into dishonest ways, not intentionally so, perhaps, not willingly, but nevertheless dishonest! Thought-



lessness, possibly even carelessness as to methods, too much haste in the endeavor to do more than one is able to do properly, lack of thoroughness, neglect to make use of instruments of precision, of advanced knowledge and up-to-date methods, all essentially dishonest practices tend to vitiate one's judgment.

The value of keen and accurate observation cannot be well overestimated. It is the straws that tell which way the wind is blowing, and so it often is in drawing conclusions, or in the matter of judgment as between two possible views or courses of action. The one whose powers of observation are ever on the alert, trained to see the slightest sign, will often almost unconsciously, by a reflex as it were, detect certain differences which to another would be entirely lost or, if noticed, would mean nothing, but to him point with unerring accuracy the way to a correct solution, it may be of a difficult problem. It is well known that now and then in the course of a physical examination the seemingly important facts elicited may tend to mislead, while some at first apparently trivial and unimportant observation, may subsequently prove to be the key to the situation. This is especially true in matters of diagnosis. I am sure we can all recall numerous incidents of this in our own experience.

What, for instance, is the significance of the sudden cessation of pain occurring in the course of an appendicitis, is it a good or bad sign? How about its relation to changes in the pulse rate? What about that suggestion of dimpling in the skin overlying an otherwise harmless appearing tumor of the breast? What is the meaning of the so-called "air-hunger" which may be the first recognizable expression of an unsuspected internal concealed hemorrhage? It is not chance, it is not having one's luck with one that enables one observer to recognize at once these from among the mass of irrelevant matter, as the facts of real import, while to another their true significance is entirely lost.

The faculty of accurate observation can be increased by acquiring the habit of examining everything within the field of vision. We fail to see many things because we fall into the easy way of passing them by without noting their presence or appreciating their significance. It was said of Charles Darwin by his son that "He wished to learn as much as possible from every experiment so that he did not confine himself to observing the single point to which the experiment was directed, and his power of seeing a number of other things was wonderful." (Quoted by Hibben.) The open-eyed vision is the prime requisite for scientific investigation. This faculty can be encouraged and developed in students by their teachers and it can be done, it seems to me, far better than in any other way, by individual instruction and bedside observation. Just here comes in the great benefit of dispensary and ward instruction in small groups, where the student can live, as it were, with the patient, and where the instructor can, man to man, discuss with the individual student the various clinical phenomena as they develop, and give to each single symptom observed its true weight and significance. Didactic lectures and teaching undoubtedly have their place in medical education, they have rendered excellent service in the past, but nothing can take the

place of the personal contact, the marked individuality which a real teacher possesses and which is unconsciously and indelibly stamped upon his pupils. What more striking example of the truth of what has just been said than is furnished in our own profession by the great Billroth who for a generation was the leader of surgical thought in Europe, and who himself during this period trained those who subsequently became themselves the heads of the best of the great German clinics. His genius is reflected to-day and may be seen and easily recognized in that one of his illustrious pupils still living, Professor Von Eiselsberg of Vienna, a shining example of the possibility of combining in the same individual the highest scientific attainment, remarkable technical skill, a charming personality and crowning all, a judgment that seems almost inspired, a living, speaking likeness of his great master.

It would appear to the writer that the career and accomplishments of this great teacher are an irrefutable argument in favor of the possibility of developing in students the power of perception, the scientific spirit, the accurate analysis, the clear judgment which makes them masters and leaders of men. For it is inconceivable that it was a mere matter of chance that brought together in his clinic a body of men of superior intellectual and professional attainments, which must of necessity and in spite of rather than because of his influence, rise to the top. Undoubtedly Billroth was an excellent judge of men, and was able to pick out of the crowd as his personal assistants, those of superior ability, and capable of the highest development. This was but an additional evidence of his own good judgment which was so abundantly shown in other ways. What an inspiration and example to all of us, teachers and practitioners as well, to follow and to emulate!

How often one sees reflected in the student the methods of thought and action of the teacher; a pet phrase, a characteristic pose, some particular idiosyncrasy which brings to mind immediately and unmistakably some strong personality under whose influence, during the formative period of his life, this particular individual has come. One is often impressed with the widespread influence exerted by the teachings of certain particular schools. Here habits of thought are established in certain well worn grooves which may be handed down from generation to generation, practically unchanged. Methods of action are thus influenced to such a marked degree by precedent and custom, that the wheels of progress may be greatly retarded, and advances, the efficacy and value of which have long since been established, indefinitely delayed. Take, for example, the question of choice of anesthetic and the method of its administration, both in this country and abroad, for the past twenty-five years, and compare methods and results. Progress on both continents has been and is still being delayed, and much unnecessary suffering and discomfort as well as an appreciable percentage of mortality induced, the direct result of too close imitation and too slavish following of discredited precedent, though often the offspring of eminently respectable parentage. How important, then, for teachers as well as schools, for the teachers primarily make the schools, to stand only for the best in everything in the educational world in the

language of the present day political vernacular, to be progressively conservative or conservatively progressive, "to prove all things, to hold fast that which is good."

The exercise of judgment, then, does away with the blind following of precedent. It is at times far better and more courageous to discard old precedent and to create new, founded upon correct observations, whether original or not, upon sound conclusions, whether at variance with preconceived notions or so-called authoritative utterances or not, than blindly to accept and supinely follow an authority, no matter how eminent. In these days of more independent thought and action, authority is not so widely recognized nor so highly respected as formerly. While this present tendency has much to commend it, there are certain evident dangers to be pointed out and avoided. In casting off the old, there is the danger of taking up with new and false gods. Fortunately, for surgeons and patients alike, there seems to be less tendency nowadays, perhaps than formerly, to follow certain fads. The days of reckless and indiscriminate operation upon the pelvic organs of the female, of nephroraphy, of gastroenterostomy, of cholecystectomy, are happily past. The stomach and the gall-bladder are still on the firing line, but the seat of war seems to be gradually shifting to the large bowel and the tonsil. There will probably always be found those whose judgment will be carried away by their enthusiasm for something new, by their eagerness to follow prevailing fashions in surgery as in dress, but it will also be found that the surgical judgment of such is as hobbled and narrow as the up-to-date style in skirts. It is truly wonderful with what facility the Aladdin's lamp of the faddist can, for him at least, instantly convert fancy into fact, and thus render an otherwise valuable member of society, or an association of such, not only of little real value, but it may be a positive menace to the human race. Witness the senseless ravings and false accusations of the various societies of the "anti's," the anti-vaccinationists, the anti-vivisectionists, etc. Nothing is more fatal to sound reasoning, nothing so productive of mental strabismus as the fad and the hobby.

As has already been suggested, judgment is not always the result of logical processes readily apparent. The line of reasoning is not always easy to follow, indeed at times it cannot be followed except by very close study and analysis of the intervening steps. There may be a sort of Sherlock Holmes' method about it, which is not readily understood by the ordinary individual, but which when carefully analyzed will show that the conclusions arrived at are no more than his, the result of happy chance or good luck, but are the inevitable result of close observation, of attention to the minutest detail, of intelligent thought, of sound reasoning. When this is done, the conclusions must inevitably follow, and they will be right or wrong just in so far as these various intellectual processes have been intelligently and correctly carried out. But there are other factors concerned. One must not be misled into thinking that it is a sort of rule of thumb, a sort of picture puzzle, the pieces of which have been cut into all sorts of fancy and bizarre shapes, and that it is simply a question of mechanically fitting them together. Not at all! Here as everywhere else imagination,

constructive imagination, is of the greatest help. As could the great Cuvier when given but a single tooth, construct the entire skeleton of a prehistoric animal, so can one in his imagination weave the entire pattern from here and there a few broken and tangled threads, supplying those that are missing, and mending those that are broken, until at last there exists in his mind a picture of the whole, clear, concise, complete, correct. The idealist, the dreamer of dreams, while not always, indeed perhaps rarely of a practical turn, is the one who of all others can penetrate deeper into the unknown, can see further into the mists of uncertainty and doubt, can make lighter the dark places of ignorance and uncertainty with the illuminating power of his imagination. "In this connection, however, attention should be directed to the condition that imagination in order to be really helpful must be at all times in touch with fact. It must represent to the mind not what fancy suggests, but what the known facts necessitate" (Hibben). The unseen is then constructed out of the determining conditions of the seen, otherwise fancy might run riot, and our judgment and hypotheses resulting therefrom, rendered correspondingly wierd and bizarre.

One of the fundamental requisites of good judgment must ever be sanity or what is known as common sense. One never expects from the insane or the foolish an opinion that is really worth anything upon any subject. Unfortunately, however, one need not be an inmate of an asylum for such unfortunates, in order to give occasional expression to opinions or exhibit actions worthy of them. Only too frequently one sees in the medical press articles expressing opinions, making suggestions, even giving advice that one would not ordinarily expect to hear outside the walls of such an institution. It is humiliating to have to admit in such an assemblage as this that some of us, and the writer feels constrained to include himself in this number, are at times guilty not only of giving advice but of performing operations, and in such a manner that in the light of further knowledge, more painstaking examination, more careful consideration, more time taken from a life overcrowded, perhaps, with the humdrum of routine and detail, puts us to shame, and which if we are truly conscientious in our work, effectually prevents any tendency toward the pride and conceit of life. Some people are by nature, perhaps, more sane, more stable, more normal in their mental processes than others. Some people are perfectly sane on some subjects and not upon others. It is extremely difficult at times to distinguish between the sane and the insane, between the sound and the unsound judgment. "Mens sana in corpore sano" is a trite but true saying.

It does not, however, necessarily follow that a sane mind and good judgment will always be found in a healthy body, nor will an unhealthy body necessarily always be found to house an unsound mind. But universal experience bears out the contention that a mind free from the distractions and worries that necessarily attend upon physical infirmities of one sort or another, or from the cares of business is in much better condition to grapple with the manifold problems of disease, of diagnosis and treatment. In our busy lives, filled to the utmost with endeavor to help and relieve others, we are prone to forget

self, a virtue always to be cultivated within reasonable limits, but the trouble with us is that we are apt to go to the limit of our endurance, and frequently beyond. Thus in our praiseworthy efforts to relieve others, and in our very self forgetfulness, we often tend to defeat the end for which we have been striving, namely, to give our patients the very best that is in us in the way of advice and treatment, which are in turn the result of our experience, ripe, wide, wisely interpreted by a brain properly working and which is not already tired out by ceaseless work and worry, and a judgment unwarped and unclouded by the pessimism engendered by a torpid liver, or a disturbed digestion.

There are negative as well as positive qualities that go with good judgment, which if not of such high order perhaps as the others, are nevertheless of great practical importance. In matters involving action, surgical treatment, operative as well as non-operative, it would be difficult to overestimate their value. In this connection, Billroth has written, "Years and experience bring in their train a certain degree of hesitancy." One frequently hears the terms radical and conservative applied to surgery and to surgeons as well as to things political. What is their meaning but that one individual or class of individuals is apt more or less blindly to do certain things under given conditions, while the other group is more likely not to do so. A favorite saying of a well-known surgeon, a man of action, but, at the same time, of unusually good judgment, was, "Nine men out of ten will know what to do under given conditions, but the tenth man will know what not to do, and he is the most valuable man of the ten." The truth of this saying, I am sure, has been demonstrated upon more than one occasion to everyone in this assemblage. The conservative surgeon is one who will take the time and the trouble necessary to observe his patient for a season sufficiently long to enable him to get some sort at least, of a comprehensive and intelligent grasp of the situation, before he is willing to express an opinion that may commit him to a definite line of action, especially when that action involves the performance of a surgical operation, however trivial it may appear. For none knows better than the experienced surgeon what far-reaching possibilities for good or for evil are lurking behind every surgical procedure. There is such a thing, of course, as over-caution which leads to inactivity and hesitation when resolution and action are urgently indicated. There are times in the experience of every surgeon when the exigencies of the case demand most instant and most radical operation, and when this becomes the height of conservatism; for example, certain forms of rapidly spreading infection, fulminating appendicitis, hemorrhage, beginning malignant disease, etc. Undue haste, however, either at the time of the operation, or in the preparation of the case, *i. e.*, operating before the patient is in proper condition, or before one is ready to cope properly with any emergency that may arise, are all evidences of poor judgment, and are equally reprehensible.

The influences working toward the production of errors of judgment, as has already been indicated, are manifold, far too many indeed to attempt to enumerate them all here. Errors of observation, failure to differentiate relevant from irrele-

vant facts, or to comprehend the whole situation, limited view, mental astigmatism, preconceived ideas, narrow-minded provincialism, human frailties, all of them play a large part in determining the results of our mental processes. We are so often swayed by prejudice. We are apt to be too much influenced by the character or personality of our patients. We so often see that which we wish to see and fail to see that which we do not wish to see; we are prone to twist the facts to suit the theory, rather than the theory to suit the facts. Thus we deceive ourselves. Our reasoning is at times faulty, "Post hoc ergo propter hoc," or "non causa sed pro causa" play far too prominent a part in the formation of our judgments. Our emotions and our passions are given too free a rein. We are so prone to forget that we do not profit as we should by our mistakes. The sacrifice is often for us in vain. As Bacon says, "The human understanding resembles not a dry light, but admits a tincture of the will, and passions which generate their own systems accordingly, for man always believes more readily that which he prefers, his feelings imbue and corrupt his understanding in innumerable and sometimes imperceptible ways." (Quoted by Hibben.) This same author in referring to the errors of judgment, due to the common frailties of human nature, has aptly styled them "idols." His enumeration is complete and classic and is as follows: "Four species of idols beset the human mind to which for distinction's sake we have assigned names, calling the first, idols of the tribe, that is, those inherent in human nature; the second, idols of the den, that is, those peculiar to each individual; the third, idols of the market, that is, those formed by the reciprocal relations of business and society, between man and man; the fourth, idols of the theatre, that is, those which have crept into men's minds from various dogmas, tradition and superstition, all of which tend to clog the mental processes and vitiate judgment."

From this very imperfect review of some of the more important factors, both positive and negative, which go to make up good judgment or to render difficult its attainment, it will readily be seen that with few exceptions, perhaps, those elements tending toward betterment and enlargement of the character and scope of our judgment are capable of development and improvement, while those idols of the mind, those forces which make for error and which tend to vitiate and render difficult our judgment may, some of them at least, be cast down and destroyed, or are by education and experience largely to be eliminated and their influence thereby markedly diminished.

Judgment is then, after all, a thing that may be, to a certain extent, at least, acquired by every one. It is assuredly better developed in some than in others, partly by divine gift, born with it, if you will, partly by education and experience. None need despair, however, by conscientious, intelligent application and study to develop the essentials and to avoid the errors, of eventually obtaining a fair proportion, at least, of that most to be desired of all qualities that go to make up a surgeon, good judgment which, if we were called upon to define in a few words, our answer would be something like this: The ability to discriminate between important and unimportant facts, between the essential and the non-essential, coupled with the



ability to draw correct conclusions therefrom. Given, as a foundation, a mind endowed by nature with an average amount of intelligence or even a little more, and of that *sine qua non*, common sense; an even disposition tinged with the milk of human kindness; a keen perception: develop this by education, fundamental, broad, comprehensive, scientific, special; add to this accurate observation; experience "by industry achieved"; a familiarity with the work of others gained through reading and by travel; time taken to properly assimilate all this and

rate it at its true value by thought and investigation; a trained hand; insight into this old human nature of ours and some knowledge of her various moods and vagaries; crown this with some of the virtues of The Great Physician, our Master and Teacher, and you have pictured before you the surgeon, fully endowed with that quality which we have but imperfectly described, Surgical Judgment, which when developed as we have seen it in the persons of some of our own teachers and friends, both living and dead, is the noblest work of God.

## TESTS FOR HEPATIC FUNCTION AND DISEASE UNDER EXPERIMENTAL CONDITIONS.<sup>1</sup>

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At this time we do not wish to discuss any of the liver functional tests proposed by earlier writers, but desire to call attention very briefly to three tests which may be of value in the study of pathological changes in the liver. We expect to publish in the near future detailed work upon which this abstract is based. A very few cases or experiments will be cited as characteristic examples of any given condition.

*Lipase* can be shown to be present in the blood plasma or serum of normal animals or human beings in a pretty constant amount. The method is briefly as follows: Four tubes are prepared, each containing 1 cc. plasma or serum diluted with 4 cc. distilled water and .3 cc. toluol to check bacterial activity. To two of the tubes is added .26 cc. ethyl butyrate, the other two serving as controls. The tubes are shaken, corked and placed in an incubator at 38° C. for 18-24 hours. They are then cooled in ice water, three drops of azolitmin added and titrated in pairs to a neutral reaction, using 1/10 normal acid and alkali. The two control tubes usually show the blood alkalinity to be .10 cc. of 1/10 normal acid and the butyrate tubes show the acid production to be .10-.20 cc. above the neutral point. This means that the total *lipolytic activity* is .20 to .30 cc. 1/10 normal solution, that the lipase of the plasma has split up the ethyl butyrate to this extent. We may speak then of a *normal plasma lipase* as .20-.30 cc. (always speaking in terms of tenth normal acid).

We have found that injury of the liver by chloroform, phosphorus, hydrazine, etc., will always cause a rise in plasma lipase. After chloroform anesthesia of 1 to 2 hours the plasma lipase in dogs will rise as high as 1 to 2 cc. 1/10 normal acid. This rise takes place during the first few hours following the anesthesia and usually persists during the second and third day following, when repair begins and the lipase falls to normal with recovery. If the animal or person is fatally poisoned the lipase will continue high until death on the fourth or fifth day. We have tested this lipase reaction in various experimental conditions where the liver is injured and find a constant rise of 2-8 times normal activity. We have followed the lipase in

human cases and believe this test may be of value in certain groups of cases.

*Eclampsia* is variously defined, but if we limit the name to those cases showing peripheral hemorrhagic liver necrosis, this test is of the greatest value. We have had the opportunity of testing the blood from several cases in the service of Dr. J. W. Williams. In a recent case the blood was obtained during the first series of convulsions and showed 1.-1.15 cc. lipase which pointed certainly to liver injury. The patient died the following day with all characteristic symptoms and autopsy (3883) showed hemorrhagic portal liver necroses as usual. The plasma obtained shortly after death showed even higher lipase readings (1.10-1.40 cc.). In pernicious vomiting of pregnancy and uremia with convulsions, the lipase shows normal readings.

Jaundice may show a slight rise in lipase, but often a normal content and obstructive jaundice of months duration may show a low lipase. Pneumonia, peritonitis, leukemias and various infections may show a rise in lipase to double normal or even more, but this will rarely confuse one. It is probable that in such conditions the excess of lipase is referable to liver changes, either liver injury or liver stimulation due to cell-split products circulating in the blood. *Yellow atrophy* of the liver surely will show a high lipase reading and in the *early stages* of liver cirrhosis the test will be of value and interest. *Liver cirrhosis* in the late stages may show a low lipase reading unless complicated with some liver necrosis.

*Fibrinogen* is normally present in blood plasma: in normal human beings it amounts to .300 to .400 gms. per 100 cc. plasma. In dogs it fluctuates more widely (.200 to .500 gms.). It has been shown in this laboratory (Whipple and Hurwitz<sup>2</sup>) that fibrinogen may fluctuate with liver injury, falling to a low level at the time of injury and returning above normal during the repair which rapidly follows. It may drop to such a low level as to be the cause of hemorrhage or a hemorrhagic tendency, because the blood clots are too soft to check hemorrhage. This explains the hemorrhages of yellow atrophy of the liver, phosphorus and chloroform poisoning, yellow fever, etc. In chronic liver cirrhosis the fibrinogen is often below

<sup>1</sup> Presented before the Association of American Physicians, Washington, May 7, 1913.

<sup>2</sup> Whipple and Hurwitz: J. Exp. M. 1911, XIII-136.

normal and at times so low as to favor hemorrhage. In such conditions the fibrinogen estimation may give valuable information. When it falls to a low level it invariably indicates a grave condition and advanced liver injury, acute or chronic.

A rough estimation of the fibrinogen is possible by causing a little oxalate plasma to clot on adding calcium. The toughness of the clot indicates in a general way the amount of fibrinogen and with some experience one can say whether the fibrinogen is much decreased in amount. The clear oxalate plasma may be heated at 59° C. for 20 minutes, the fibrinogen which is precipitated, collected by centrifugalization, washed with cold and hot water, dried with alcohol and washed with ether. This precipitate is then collected in a weighed Gooch crucible, dried at 120° C. and weighed. Twenty cubic centimeters of plasma are best used for each determination. This heat method is quite accurate except when the fibrinogen is very low; under these conditions it gives too low an amount and if possible the plasma should be clotted with fresh serum and the fibrin weighed after washing, etc.

In certain cases of hepatic cirrhosis we have reported a very low fibrinogen index (Whipple\*)—a drop to .050 gm. or even less. This is not an invariable finding in this disease, but when present is of the gravest prognostic import.

In human cases of fatal late chloroform poisoning the fibrinogen during the last two days of the intoxication may drop to .048 gm. and finally to .034 gm. per 100 cc. plasma (autopsy 3726). When the liver is exposed to minor injuries it may respond with an over-production of fibrinogen, which may rise even to 1 gm. per 100 cc. plasma. This minor injury may be looked upon as a stimulus and the high fibrinogen content found in pneumonia, septicæmia, peritonitis, etc., can be explained by the action of certain substances upon the liver epithelium. These substances may be derived from disintegration of the body cells or foreign cells and when very abundant may be able to cause degeneration and even liver cell necrosis, but in lesser amounts may be imagined to have a stimulating action (or irritative effect) upon the liver.

*Phenoltetrachlorphthalein* is a drug which is excreted by the liver into the bile. Abel and Rowntree<sup>4</sup> reported a study of this drug in connection with work on subcutaneous purgatives. Rowntree,<sup>5</sup> who was familiar with the characteristics of phenoltetrachlorphthalein and had established the normal excretion in dogs with biliary fistulæ, suggested that we use the drug in our work with abnormal hepatic conditions. The drug which was used had been supplied to Rowntree by Professor Orndorff of Cornell University. A preliminary series of experiments on dogs, whose livers had been acutely injured by various means, showed that there was a remarkable decrease in phthalein output during the period of liver injury. Rowntree, Hurwitz and Bloomfield then proceeded to apply the test to patients in the wards, since which time the experimental and clinical work has been going on side by side with concordant findings. More careful experiments show that there is a very striking parallelism between the

amount of liver injury and the output of phthalein. The drug was given subcutaneously in the first experiments, but it was found that the *intravenous* injection of the sodium salt offered many advantages over the oil method.

The procedure which gives best results in the experimental work may be outlined as follows: Female dogs are used when possible to facilitate catheterization and are given .100 gm. phthalein when weighing between 10 and 20 lbs.—200 gms. when over 20 lbs. The solution is injected intravenously, given usually in the forenoon. The dog is then given water (200-300 cc.) by stomach tube to promote diuresis. After a period of five or six hours the urine is collected and a purge given, usually magnesium sulphate and croton oil in sufficient amounts to give several semi-fluid stools. The feces are collected the next morning and experience shows that no phthalein can be obtained by subsequent purgation. It is important to obtain brisk purgation, as it is known (Abel and Rowntree) that the drug is absorbed from the large intestine and must be swept out rapidly to give a uniform result. Delay of purgation for 24 hours will drop the phthalein output from normal (40-50 per cent) to 30 per cent or even a little lower.

The method of extracting the feces is relatively simple and not time consuming. The total feces are diluted to 1 or 2 liters as may be necessary in collection from the metabolism cages. The mixture is made alkaline with sodium hydroxide (5-10 cc. of a 40 per cent solution) and shaken until a good uniform mixture is obtained. One-tenth of this is taken and diluted to 500 cc. with water, 3 to 4 cc. of 40 per cent sodium hydroxide added and the mixture thoroughly shaken. Of this second solution are taken 100 cc. for precipitation with basic lead acetate (5 cc. of a saturated solution). After a few seconds a curdy precipitate comes down and the solution is then made up to 200 cc. with water containing 4 cc. of sodium hydrate (40 per cent). On standing the supernatant fluid shows a clear phthalein color and with filtration gives a solution which can be read directly in a colorimeter<sup>6</sup> against a standard solution—10 mg. phthalein to the liter.

This procedure in our hands gives a very uniform phthalein output in the feces of normal dogs, 35-50 per cent with .100 gm. injections and 40-55 per cent with .200 gm. doses. The same dog may show fluctuations within these limits depending in part upon purgation and collection of feces. The drug given in these doses does not come through in the urine of a normal dog. Phthalein given by stomach and collected in the feces in the usual way will average 60-65 per cent, showing the amount of drug which is lost through contact with the intestinal mucosa and collection of the feces. When the phthalein is added to large amounts of feces it can be recovered completely (97-100 per cent) by the method outlined above.

This shows that only 10-15 per cent phthalein is lost from the time the phthalein is injected intravenously until it is poured out by the liver in the bile into the duodenum. This indicates a remarkable degree of secretory activity and specificity of the liver epithelium.

\* Whipple: Arch. Int. M. 1912, IX-365.

<sup>4</sup> Abel and Rowntree: J. Pharm. and Exp. Therap. 1909, I-231.

<sup>5</sup> Rowntree: J. Am. A. Asso., 1910, LIV-344.

<sup>6</sup> R. and G. modification of the Autenreith-Konigsberger colorimeter, which reads directly in per cent.

When *liver injury* is produced by chloroform, phosphorus, hydrazine or other agents there is a drop in feces output to 20 per cent, 10 per cent or even a mere trace, depending on the extent of the liver injury, and the *phthalein* now comes out in the *urine*  $\frac{1}{2}$ -4 per cent. The mechanism of liver repair is familiar and with this return to normal the phthalein output comes slowly back to normal. This is illustrated by a simple type experiment.

*Dog 12-48.*—Strong female fox terrier, 14 pounds.

April 3, 12 m. Phthalein .100 gm. intravenously. 5 p.m. Urine. Phthalein negative. Purged.

April 4, a.m. Feces collected. Phthalein 47 per cent.

April 8, 11 a.m. *Chloroform anesthesia* 1½ hours. At end of anesthesia given *phthalein* .100 gm. intravenously. 5 p.m. Vomitus and urine. Phthalein 12 per cent.

April 9. No feces. Dog vomits purges.

April 10, 10 a.m. Fluid feces. Phthalein 7-9 per cent. 12 m. Urine contains bile pigments. Phthalein negative.

April 10, 3 p.m. Phthalein .100 gm. intravenously. 5 p.m. Urine 100 cc. Phthalein  $\frac{1}{2}$  per cent. 7 p.m. Urine 100 cc. Phthalein 1 per cent. 9 p.m. Urine and vomitus. Phthalein  $\frac{1}{2}$  per cent.

April 11, 9 a.m. Urine plus vomitus. Phthalein 2 per cent. 4 a.m. Abundant feces. Phthalein 25 per cent.

April 12. Dog is improving rapidly and eats well. Weighs 12½ pounds.

April 15, 1 p.m. Phthalein .100 gm. intravenously. 4 p.m. Urine. Phthalein 0.1 per cent. Purged.

April 16, 10 a.m. Feces abundant. Phthalein 45 per cent.

The average amount of injury done to a dog's liver by two hours chloroform anesthesia is a central necrosis involving about two-fifths of the parenchyma of each lobule. We may assume some such injury in the above case and the prompt drop to less than half phthalein output with return to normal within a week is to be expected from the knowledge of the process of repair following such an injury (Whipple and Sperry<sup>7</sup>). It is possible to injure the liver so severely that the phthalein output may drop almost to zero, and in a majority of such cases the injury will lead to the death of the animal. The following experiment shows a severe liver injury followed by recovery, the phthalein falling about to zero:

*Dog 12-90.*—Small mongrel male, weight 11 pounds.

April 10, 3 p.m. Phthalein .100 gm. intravenously.

April 11, 10 a.m. Feces abundant. Phthalein 43 per cent.

April 14. *Hydrazine sulphate* .100 gm. given subcutaneously.

April 15, 1 p.m. Phthalein .100 gm. intravenously. *Hydrazine sulphate* (2d dose) .100 gm. subcutaneously. Weight 10 pounds. 5 p.m. Urine. Phthalein  $\frac{1}{2}$  per cent. Vomited, purged.

April 16, 9 a.m. No feces. Vomits purges. Dog looks very sick. Urine and vomitus. Phthalein 4 per cent. 4 p.m. Feces small amount. Phthalein mere trace (2 per cent.).

April 17. Jaundice is evident in skin. Dog very dull. 11 a.m. One soft stool. Phthalein mere trace.

April 18, 10 a.m. Dog slightly better. Urine shows large amount of bile and faint cloud of albumin. Weight 8½ pounds. 2 p.m. Phthalein .100 gm. intravenously.

April 19, 9 a.m. Cage urine. Phthalein (2 per cent), one fluid stool. Phthalein 8 per cent.

April 22, 12 m. Urine free from bile and albumin. Dog is

very much better. Phthalein .100 gm. intravenously. Weight 9 pounds. 5 p.m. Urine. Phthalein 2 per cent. Purged.

April 23, 10 a.m. Feces abundant. Phthalein 35 per cent.

It is obvious that this test can be of little value in *obstructive jaundice*, but it is interesting that little if any of the drug will escape in the urine. When the phthalein is given shortly after ligation of the common bile duct—the same or following day—the urine will show but a trace of phthalein. When the obstruction has been present days or weeks the phthalein will appear in the urine (1-2 per cent) and we believe in each case this is dependent upon true liver injury. When the phthalein remains in contact with the body tissues for 24-48 hours in obstructive jaundice, it is changed to some substance which is not recognizable, but traces can be found in the gall bladder three to six days after a phthalein injection in obstructive jaundice. The drug is not secreted by the intestinal mucosa and in complete obstructive jaundice there is never a trace of phthalein in the feces.

Passive congestion of the liver cannot be produced in dogs to the extreme degree seen in human cases with broken cardiac compensation. However, it is possible to produce passive congestion of the abdominal viscera by means of stitches placed in the vena cava inferior just above the diaphragm, narrowing the lumen to 1 or 2 mm. in diameter (McClure). Such animals develop extreme ascites, collateral circulation, enlarged spleen, etc., and they show a slight decrease in liver excretion of phthalein with no escape in the urine.

The Eck fistula produces a liver which has a scanty blood supply, chiefly arterial, and the liver undergoes a slow atrophy with some fatty change in the early stages. These dogs show a decrease in phthalein output (20-30 per cent) and the urine contains 0.5-3 per cent phthalein. This indicates a certain degree of liver insufficiency and liver injury. It is interesting that an Eck fistula dog living over a year has an output which has returned practically to normal and only traces of phthalein in the urine, indicating that the liver has regained its functional balance. The clinical features of these animals support this interpretation.

It is clear that phenoltetrachlorphthalein gives promise as a functional liver test. It is excreted in the bile through activity of the liver epithelium and not the bile duct epithelium. Any agent which injures the liver parenchyma or interferes with its functional activity will cause a drop in phthalein output in the feces. Acute liver injury also is associated with an escape of phthalein in the urine, we believe due to a modification of the phthalein through the agency of the injured liver cells, so that it passes through the renal epithelium. Clinical material is being studied by Rowntree, Hurwitz and Bloomfield. The details of drug preparation, injection and collection will appear shortly with a report on these clinical studies. It may be said that the findings in clinical cases which have been supported by autopsy or exploration are in harmony with the experimental observations.

It is probable that with accumulated experience in the interpretation of the varied findings in these three tests, we may be able to define more and more accurately the anatomical and functional abnormalities of the liver.

<sup>7</sup> Whipple and Sperry: Johns Hopkins Hosp. Bull., 1909, XX-278.



# MULTIPLE CONGENITAL OSTEOCHONDROMATA WITH DEGENERATION OF CRANIAL NERVES AND MUSCULAR DYSTROPHY.

## REPORT OF CASE.

By THOMAS R. BOGGS, M. D.,

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Congenital exostoses and enchondromata are among the rarer skeletal anomalies and have attracted much attention from the clinical observer and pathologist. The literature of the subject is voluminous and has been satisfactorily reviewed by others (Schmidt, Frangenheim). The writer will therefore limit himself to a brief statement of what is generally accepted as to the occurrence and histogenesis of the condition with a description of a case with unusual associated features.

While very few observations on the new-born are recorded, such cases have been described by Murchison and Syme, Vix, Koester, Myers, and others. And there is much reason to accept the view that these tumors are truly congenital and due to abnormal anlage in the intermediary cartilages (v. Bergmann).

The anomaly is, in many cases, clearly hereditary, and the heredity may be immediate from parent to child, or miss a generation. Likewise, an individual with exostosis may have descendants, with enchondroma, or vice versa. Or, either type may show mixed heredity in the descendants. The incidence is greatly preponderant in the male members of such families.

The causes of the anomalous development are still obscure. Several authors have noted thyroid hypoplasia, cystic goitre, or Basedow's disease in their cases. Poor development of the mental and sexual functions has also been remarked. Inter-marriage of relatives has been suggested by some authors as a possible factor.

The exostoses are more common on the long bones, those of the lower extremities being more frequently involved than the bones of the arms. Small exostoses are often found on the ribs, especially near their heads. The feet and hands, as a rule, show few exostoses, while the pure enchondromata are most frequent on these parts. In general, the distribution of the growths is symmetrical, although exceptions occur in which one-half of the body, or one limb, is involved. The cranial bones of periosteal origin are free from this type of anomaly, but exostoses have been found at the sutures.

The characteristic deformities produced are: distortion and shortening of the long bones, with dwarfism, the trunk being better developed than the extremities. The sites of election for the tumors on the long bones are metaphysis, epiphysis, and diaphysis in order of frequency. The size of the exostoses varies from a few millimeters to many centimeters in diameter. In the forearm and leg the bones are often bridged by exostotic processes.

Bowing of the radius, with or without dislocation of the elbow, is quite frequent, due to the overgrowth of the radius stimulated by the tumor at the epiphysis. Bursæ at the outer

portion of the tumors are common and may be large and contain floating bodies.

The cartilaginous covering of the exostoses is irregularly distributed and disappears during puberty, when growth of the tumor ceases. Later some absorption may take place; in a few instances the tumors have entirely disappeared. The structure, histologically, is very like that of normal bone. Primary necrosis and large areas of cystic degeneration are quite uncommon. Sarcomatous metamorphosis has been observed very rarely.

The tumors themselves are, for the most part, harmless, and they are not painful. But they may produce grave symptoms from pressure on contiguous blood vessels and nerve trunks. The skin over the exostosis may become necrotic from pressure and lead to a severe local abscess or a general infection. In women the presence of exostoses in the pelvis may interfere with child-bearing. Exostoses may hamper the movement in important joints.

Very little is known of the association of other congenital anomalies with exostosis. Several cases of extensive spinal cord lesions have been noted (Oberndorf), and some writers assert that anterior horn cell degeneration in the cord causes trophic changes in the bones, leading to exostosis.

The patient, W. K., white, 23, single, teamster, was admitted to the City Hospital, July 20, 1912, complaining of weakness of the legs.

On account of absolute deafness, the history was difficult to obtain, and imperfect.

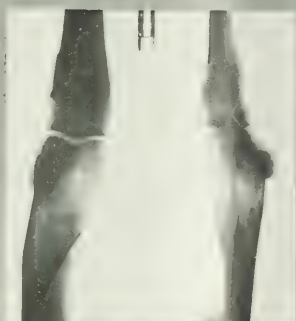
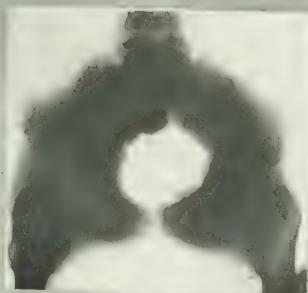
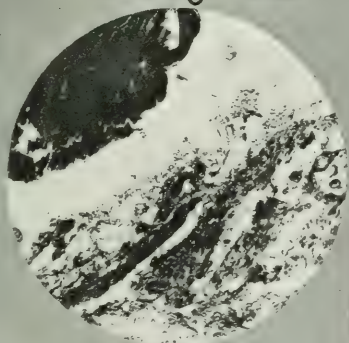
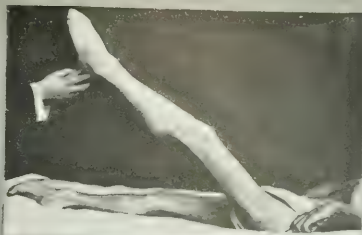
*Family History.*—Father, who was killed in an accident, had "bony lumps" on both legs. Mother dead, cause unknown to patient. Three sisters and one brother living and well. None have any bone tumors or other congenital defect.

*Past History.*—The patient does not remember any illness until present illness. Sisters say he was born with lumps on legs and arms and, while never very active, was healthy and able to work. At the time they last saw him, two years before admission, he was apparently well and not deaf.

He denies any venereal infection. Has always been thin and had worked as teamster until about eight months before admission, when his legs became too weak.

*Present Illness.*—Legs have been weak for some time; he had to give up work about six or eight months ago. Did not feel sick. He does not know when deafness came on, but not more than a year or so ago. No pain or discharge from ears preceded or accompanied it. Says he can see as well as ever and that his legs are no worse.

*Physical Examination.*—Medium-sized, under-nourished man. Seems fairly bright and intelligent. Absolutely deaf, but can read the lips a little. Reads large print or writing very slowly and not altogether with full comprehension. Voice is low pitched, flat and husky, does not volunteer any remarks. Skin rather dry and rough, faint diffuse, brownish pigmentation.



1-6. Photographs showing distribution of tumors.  
 4-5-6. Attitudes in rising from floor (dystrophic climbing)  
 7. Section of excised muscle showing atrophy.  
 8. Skull. Normal sella turcica.

9-16. Radiograms of skeleton.  
 11. Characteristic bowing of overgrown radius.  
 12. Large mass in the pelvic strait.  
 14. Tumor on left fibula showing cystic changes.





Eyes: Deep set. Sclera visible all around iris, giving a peculiar stare. Sight from Graefe. Winking normal. Movements of eyeballs and lids normal. Pupils equal, react to light and accommodation. Fundi show clear-cut, pale discs with pallor more marked to temporal side. Veins and arteries small. No exudate or hemorrhages. Double optic atrophy of moderate grade. Visual fields show extreme general contraction to a small area about each fovea.

Ears: Apparently deaf for air conduction. Cannot satisfactorily test for bone conduction, as patient does not understand what is wanted. No spontaneous nystagmus. After irrigation with cold water there is normal nystagmus response on both sides, showing that both vestibular nerves are intact. External ears and tympani apparently normal.

Nose, pharynx, tonsils, and larynx normal. No general or local glandular enlargement.

Thyroid: The neck is thin and the tracheal rings easily felt from the cricoid down below episternal notch, but no thyroid isthmus is palpable; lateral lobes cannot be made out.

Lungs: Slight impairment to percussion at both apices, generally enfeebled breath sounds, but no râles of any kind.

Heart: Normal in size and rhythm, no murmurs. Pulse good volume, regular, 70 to minute. No marked sclerosis. Systolic blood pressure 100 mm. (Tyco's).

Abdomen: Rather scaphoid; no enlargement of liver or spleen. Colon seems rather full of pasty feces; large bony mass in left iliac fossa.

Genitalia: Normal. Hair normally developed over body.

The patient stands with legs wide apart, and walks with a steppage gait. When placed prone on the floor he gets up with difficulty, climbing up his legs like a dystrophic child. (See photographs.)

Musculature: Facial muscles and tongue normal. Considerable atrophy of shoulder girdle groups, and intrinsic muscles of hands. All the normal movements preserved. No fibrillation. Muscles of trunk seem small but normally active. Wasting of thigh and leg muscles on both sides, more marked on left. Extreme talipes equinus. There is marked weakness, but no paralysis. The peroneal and anterior tibial groups very much wasted. No fibrillation.

Electric Examination: Marked decrease in electric excitability without qualitative changes; *i. e.*, no reaction of degeneration. Suggests condition similar to dystrophy, or progressive muscular atrophy.

Sections of left tibialis anticus show marked atrophy with some hypertrophic fibres and supernucleation.

Nervous System, General: Deep reflexes slightly exaggerated. Plantar response (Babinski) normal. No clonus. No sensory changes. No ataxia. No spasticity.

Bones: Skull small, but normally proportioned. Mandible normal. No exostosis made out.

Spine: No abnormalities made out, except that apparently there are six lumbar vertebrae and one less in sacrum.

Pelvis: Thickening of os pubis, huge exostosis projecting from left under side of ilium. Clavicles thickened at inner ends. Scapulae and ribs normal to palpation.

Arms: Upper third of both humeri much thickened and irregular. Hand normal. Large, irregular exostoses, size of a man's fist, project from inner aspect at junction of upper and

middle third. These are very hard, with small flaccid bursae at outermost points of each, containing a few bean-sized bony, or calcareous, bodies. The lower ends of humeri seem normal. Exostoses on both ends of the forearm bones. Radii overgrown and bowed outward. Small spur on each first metacarpal. Some irregularity at bases of first phalanges. Other bones of wrists and hands normal.

Legs: Upper ends of thighs much thickened, several spine-like outgrowths on each shaft. The fibulae show very large, bony tumors at the head, the left larger. These are irregular, firm, and no bursae are felt. The bony masses, as large as an orange, contrast strangely with the atrophic legs. Exostoses are present about the malleoli on both sides. Marked talipes equinus, bilateral, but no large exostoses are felt on bones of the feet.

Urine: Faint trace of albumin and a few hyaline casts. No Bence-Jones protein.

Blood: R. B. C. 6,400,000; Hb. 90 per cent; W. B. C. 8,300. Differential count shows normal formula. No anisocytosis. No abnormal constituents.

Wassermann reaction negative.

Spinal Fluid: Pressure 160 mm. (spinal fluid). Slightly yellow, 17 cells per cu. mm. of small mononuclear type. Noguchi butyric acid test positive. Wassermann reaction negative.

Stools: No abnormal constituents.

X-ray Examination: Rarefaction of bones, with numerous exostoses of osteochondromatous type, symmetrically disposed on extremities and on pelvic bones. The largest tumor at the head of left fibula, is apparently cystic. The skull seems entirely free from exostoses and the sella turcica is normal in size.

Summary: Young man with multiple congenital osteochondromata (father similarly affected).

Thyroid Atrophy. Later, development of degeneration in acoustic and optic nerves; and muscular dystrophy.

No similar cases have been found in searching the literature. The case probably represents congenital defects in the nervous system, as well as in the bones. The X-ray photograph of the skull shows a normal sella turcica, and the escape of the vestibular nerves on both sides, while the acoustic nerves are completely degenerated, make it certain that the nerve changes cannot be due to pressure from exostoses. Whether the thyroid atrophy has any bearing on the bony or nervous changes cannot be more than suggested.

Special thanks are due to Dr. H. M. Thomas for his interest in the neurological examinations, to Dr. S. J. Crowe for his notes on the ears, nose, and larynx, and to Drs. F. H. Baetjer and Charles Waters for the numerous skiagrams.

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# THE PATHOLOGY OF SYPHILITIC AORTITIS WITH A CONTRIBUTION TO THE FORMATION OF ANEURYSMS.

By M. C. WINFERNITZ, M. D.

(From the Pathological Laboratory of The Johns Hopkins University.)

WITH THREE FIGURES.

The characteristics of syphilitic disease of the aorta, are now well recognized. Among the still unsettled questions in this relation is the formation of aneurysms. While it is contended by a few that aneurysms form in the stage of acute gummatous degeneration, the general opinion is that they form later, after the medial fibrosis has taken place. The recent occurrence of an early lesion of syphilis of the aorta with minute aneurysms lends positive evidence to the first view.

The following notes will review in brief sequence the historical and pathological development of the subject of syphilis of the aorta; the differentiation of ordinary arteriosclerosis from syphilitic aortitis; the specific nature of syphilitic aortitis; its occurrence as a congenital lesion and, finally, the relation of the lesion to the formation of aneurysms.

*Historical.*—Until recently the conception was general that syphilis only affected the aorta inasmuch as it was an important etiological factor for the usual arteriosclerotic process, *i. e.* endarteritis chronica deformans, nodosa or atheroma. Especially from the clinical side was this emphasized. The early age at which aneurysms often occurred, a decade or more before the age of arteriosclerosis, led to the belief that syphilis brought about a markedly severe and early sclerosis. The association of syphilis with aneurysms was emphasized by Welch<sup>1</sup> on account of the numerous aneurysms which occurred in young people in the English army. Antisyphilitic treatment was without beneficial results upon aneurysms (Fournier) except in a few isolated cases (Verdie see Benda). Statistically varying numbers of aneurysms from 95 per cent (Heller<sup>2</sup>) to 18.75 per cent (v. Hanseemann<sup>3</sup>), were found associated with syphilis.

Such authors as Virchow<sup>4</sup> and Welch<sup>1, 5</sup> even though they realized that there was an intimate association between syphilis and aneurysm production only believed that syphilis brought about an early and marked sclerosis of the usual type, from which the aneurysms developed secondarily. On the other hand, definite active or even gummatous lesions of the aorta have been described both with and without aneurysms, as for instance, the case of Wilks<sup>6</sup> in 1863 associated with aneurysm, and that of Wagner<sup>7</sup> unassociated with aneurysms.

The first description of the specific appearances particularly the macroscopic appearances of syphilitic aortitis, dates back to 1866 (Wagner<sup>7</sup>) and 1873 (Hemlstedter<sup>8</sup>). These authors recognized that the process was different from the usual atheromatous changes, but they did not realize its specific nature, and Hemlstedter though describing the microscopic lesions of the media considered that they were the result of mechanical rupture of the elastic lamella with replacement fibrosis. Hertz<sup>9</sup> likewise described the macroscopic lesions in

1873 and Vallin<sup>10</sup> in 1879, but they considered the lesion a simple form of arteriosclerosis. Heiberg<sup>10</sup> in 1876 not only described the macroscopic but also the microscopic changes. He recognized the latter and considered them as analogous to the changes described by Köster, *i. e.* a cellular infiltration in the media and about the vasa vasorum and partial obliteration of the vasa vasorum. Heiberg considered that the localized zones of cellular infiltrations might be recognized as miliary gummata. Soon after this Laveran<sup>11</sup> described a similar case and independently noted the presence of miliary gummata in the media. In 1880 Snow<sup>12</sup> recognized an important characteristic of the specific aortic lesion, *i. e.* obliteration of the mouth of one of the large vessels in a case of aortic aneurysm in a young syphilitic girl. Köster<sup>13</sup> in the same year gave a detailed description of the specific lesion. He called it a mesoarteritis and considered syphilis as the etiological factor. He did not regard the change as a specific syphilitic process, inasmuch as he did not think that it differed from the usual arteriosclerotic process except in intensity and extent of involvement.

Despite the above and other valuable preliminary reports, the real significance of the specific syphilitic lesions of the aorta and their importance in the etiology of aneurysms was only realized after the numerous contributions by the Kiel school. These writers opposed, and after many years overthrew the theory that syphilis was one of the factors in the production of the ordinary forms of arteriosclerosis, and established the gross and microscopic lesions which to-day are recognized in the vast majority of instances at least to be the result of a typical gummatous syphilitic lesion and quite distinct from other forms of arteriosclerosis.

Döhle's<sup>14</sup> first communication (1885) was the beginning of a series appearing from the Kiel laboratory. He described the lesions occurring in a 25-year-old man with outspoken hues of various organs. The aorta, particularly in the ascending and to a lesser extent in the descending thoracic portion showed larger and smaller ballooning of its wall. There were only a few yellowish elevations in an otherwise normal intima. Microscopically there was a diffuse infiltration of round cells in the media; in places masses of round cells and blood vessels occupied clefts in the media; here and there bands of fibrous connective tissue were found running through the media and joining the adventitial and intimal coats, retracting the latter which otherwise was very little changed. The adventitia showed inflammatory changes similar to those described in the media, although somewhat less pronounced. Döhle concluded that the cellular infiltrations in the media were gummata which subsequently became converted to scar

tissue and that the entire process except the intimal thickening which he regarded as a diffuse proliferating endarteritis was peculiar to syphilis. Döhle's<sup>20</sup> second report in 1895 included two similar cases. He concluded from their study that the lesion was recognizable macroscopically by radiating scarred depressions and indentations of the intima, and that these were caused by luetic lesions of the media and adventitia.

A series of papers by Backhaus,<sup>21</sup> Philips,<sup>22</sup> Moll,<sup>23</sup> Isenberg<sup>24</sup> and Heller<sup>25</sup> supported Döhle's view. Heller sums up the situation in 1903 as follows: Macroscopically there are always scar-like depressions and furrows on the inner side of a conspicuous syphilitic aortitis. Microscopically, above all there is a cellular infiltration in the media, and it is not rare to find multinucleated giant cells and necrotic areas in these proliferations which may be called miliary gummata. Occasionally large caseous areas occur. From the cellular proliferations fibrous scars arise. Secondly, the intima may be thickened but this thickening has no tendency to undergo atheromatous degeneration, and has, on the contrary, a stiff scar-like contracted character. The adventitia is variably affected. It may be sclerotic and the vasa vasorum may be entirely occluded. Heller says the diagnosis of the specific lesion is often made difficult, on account of the frequent combination of a syphilitic with an ordinary atherosclerotic process.

This view of syphilitic disease of the aorta as conceived by Heller and his school was accepted by a large number of writers (Buchwald, Jacob, Crooke, Belfanti, Abramow, Heiberg, Puppe, Rasch, Straub, Benenuti and others cited by Chiari<sup>26</sup>). Rasch<sup>27</sup> pointed out that the intimal thickenings were not yellow, but a dull gray and that the lesion was confined most often to the thoracic aorta. Straub<sup>28</sup> added that the process was often most intense at the origin of the larger branches, as in the arch and that the process was often confined to the thoracic aorta, sometimes extending to the upper portion of the abdominal aorta. Further the lower edge of the process often ended abruptly and had a sharp line of demarcation.

#### THE DIFFERENTIATION OF ARTERIOSCLEROSIS FROM SYPHILITIC AORTITIS.

The following description and differentiation of the usual form of endarteritis chronica deformans (arteriosclerosis) of the aorta and aortitis of syphilitic origin may be abstracted from Chiari's masterful description.

Arteriosclerosis begins in the intima with swelling of the tissue, increase in local cells and fatty degeneration of these. Often it seems as though the fatty change may have been primary. Following these changes there is an increase in the connective tissue of the intima which has a tendency to undergo a hyaline, fatty or mucoid degeneration, necrosis or calcification. Frequently there is a new formation of elastic tissue. At first the media and adventitia are normal, but later these layers also become involved. The inner layer of the media undergoes a degeneration similar to that in the intima and in its outer layers there may be a moderate pro-

liferation of blood vessels together with a mild grade of cellular and connective tissue proliferation. In the adventitia there may be a round cell infiltration along the course of the vasa vasorum and the latter may show an endarteritis proliferans. The inflammatory changes of the intima and media, however, are confined within narrow limits and Chiari says, he has never seen any degree of mesoarteritis or periaortitis in pure endarteritis chronica deformans. Under specific conditions proliferation in the media may occur in localized areas, for instance, below a large, fatty or calcified plaque in the depths of the intima, and pressing on the media. In such instances there is a proliferation of connective tissue through the media towards the plaque which acts like a foreign body. Chiari could not confirm Köster's idea that the intimal thickenings are always secondary and the result of a mesoarteritis arising from the vasa vasorum, nor could he agree with Martin that there is always an endarteritis proliferans of the nutrient vessels resulting in a fatty degeneration and inflammatory proliferation of the intima. He agrees, however, with Virchow that there is a "parenchymatous proliferation" in the intima without there being any appreciable involvement of the blood vessels. He also agrees with Marchand that the early changes in arteriosclerosis are associated with a nutritional disturbance of the vessel wall which manifests itself in a swelling, thickening and sclerosis of the intimal tissue, an increase and subsequent degeneration of the cellular elements frequently followed by partial necrosis and calcification. In other instances the most conspicuous change is an indurative thickening of the intima. Both the degenerative and inflammatory involvement of the media and adventitia are secondary. They are in part a reaction against the degeneration, and in part play the rôle of a reparative process. The etiological factors for this type of aortic change are numerous and are associated with intimal or medial damage caused by mechanical, infectious, and other agents.

The above series of changes are in marked contrast with those that occur in syphilis. Here the affection of the adventitia and media plays the title rôle, and appears to be primary while the intimal thickening only develops secondarily. Chiari says that microscopically syphilitic aortitis is similar to the above described arteriosclerotic process with the following peculiarities: There is less tendency for the intimal proliferation to undergo regressive metamorphosis. The intimal changes in comparison to those of the adventitia and media are often strikingly slight or in the early stages of the disease entirely lacking. The lesion is further identified by the frequent occurrence of furrows and wrinkles on the inner side of the aorta and finally by its regular occurrence in the ascending portion of the aorta, descending on the one hand to the semilunar valves and on the other across the arch and the descending aorta rarely as far as its abdominal portion. The diseased process frequently stops abruptly above the abdominal aorta.

Microscopically the medial changes are the most striking. They consist of inflammatory areas which appear partly as accumulations of round cells, partly as vascular granulation



tissue. These zones extend from the adventitia through the media, towards the intima and run at right or oblique angles to the axis of the vessel. Giant cells similar to the Langhans cells found in tuberculosis may be present in the inflammatory zone. The granulation tissue surrounding pieces of necrotic media may also contain giant cells, partaking more of the nature of foreign body giant cells. The fibrous connective tissue arising from these areas of necrosis tends to contract and in this way produces the depressions and wrinkles of the surface. The adventitia shows an inflammatory reaction. The younger areas appear as masses of round cells and granulation tissue situated along the vasa vasorum while the older manifest themselves as dense fibrous connective tissue. The vasa vasorum show an endarteritis proliferans. The intima presents a variable picture. It may be unchanged, moderately or greatly thickened. The latter has little tendency to undergo regressive metamorphosis; on the other hand it may present an ordinary endarteritis chronica deformans, *i. e.*, thickenings with marked fatty degeneration and calcification.

Chiari believes that this second type of aortic disease is a distinct anatomical form, and should be separated from the usual types of chronic deforming endarteritis. He concludes from his studies that absolute scientific security in the diagnosis as luetic of such a productive mesaortitis will only be arrived at when we have more complete knowledge of the virus of syphilis. Further that he would not desire to exclude the possibility that a similar anatomical picture may be brought about by a different etiological agent. Still he considers that the findings of a productive mesaortitis should be regarded primarily as a syphilitic process.

Many were skeptical concerning the specificity of syphilitic mesaortitis. Heine<sup>22</sup> comments that he does not consider every mesaortitis as syphilitic, and that after the scars have formed he thinks there is no longer any criteria concerning their etiology. Ribbert<sup>23</sup> also did not consider the proof sufficient and Marchand<sup>24</sup> says that while it is true that many aneurysms occur in syphilitics, attempts to demonstrate changes in the blood vessel wall of a specific luetic nature are not always attended with good results, as they may not be present in the later stages. He believes that similar lesions may occur without lues, but grants that probably most of them are luetic.

With the discovery of the *spirochæta pallida* as the etiological agent for syphilis a more direct means has been put at our disposal for the determination of the specific cause of this disease of the aorta. Unfortunately here as in the other tertiary lesions of the disease difficulty has been experienced in demonstrating the organisms. In favorable instances and in earlier lesions they are present in large numbers in the areas of round cell infiltration and necrosis of the adventitia and media, and have been demonstrated in such instances by Reuter,<sup>25</sup> Schmorl,<sup>26</sup> Benda,<sup>27</sup> Wright and Richardson<sup>28</sup> (5 cases), Wright<sup>29</sup> (3 cases) and Klotz.<sup>30</sup>

On the other hand the Wassermann reaction has been of great aid in demonstrating the specific luetic nature of mesaortitis. To quote from Pearce,<sup>31</sup> for instance, the combined statistics of Noguchi, Swift, Bruch, Kaplan, etc., show

that the reaction was positive in from 63 to 89.9 per cent of 1878 cases of tertiary syphilis while it was only positive in from 0.3 to 1.1 per cent of 5,946 non-syphilitic cases. With this as a basis Pearce has collected the results of the Wassermann reaction in a large number of cardio-vascular cases and finds that it is positive in 66.6 per cent of aneurysms 69.6 per cent of aortic insufficiencies 23.5 per cent of other valvular lesions, and in 81.45 per cent of cases of mesaortitis. From these results Pearce correctly concludes "that the general theory concerning the association of mesaortitis, aortic insufficiency and aneurysm, and the relation of these conditions to syphilis is supported."

One of the more interesting recent findings and one which at least lends absolute evidence to the above idea that mesaortitis is frequently caused by syphilis, if even further reaching conclusions may not be drawn, is the fact that a similar lesion of the aorta has been described in congenital syphilis. This lesion has become established through the work of Hasselbach, Wiesner,<sup>32</sup> Rach and Wiesner,<sup>33</sup> Klotz,<sup>34</sup> etc. The congenital lesion seems quite analogous to the disease in the adult.

It appears from the studies of the congenital lesions that every syphilitic aortitis is not necessarily a mesaortitis since in several cases of fresh congenital syphilitic aortitis huge numbers of *spirochæta* were demonstrable in all the tissues of the aorta, particularly in the intima. The various coats of the aorta were affected by the presence of the organism and had reacted to its irritation. Mesaortitis may be the most common picture of syphilis of the aorta, still it is not the only type and therefore mesaortitis and syphilis of the aorta may not be considered as synonymous.

The demonstration of the *spirochæta pallida* in the aorta in congenital lues is of interest. Rach and Wiesner examined 27 cases of congenital lues; 16 per cent of these showed typical lesion of the aorta, but in only four were the organisms demonstrable. The organisms were so situated that no relation between the local lesions and the position of the organisms could be established.

#### THE RELATION OF THE DISEASED PROCESS IN THE AORTA TO THE FORMATION OF ANEURYSM.

Helmstedter<sup>10</sup> and Mahchof<sup>35</sup> considered the basis for their questionable disease of the aorta to be a primary rupture of the elastica, while Köster, and others believed that it was the result of an inflammatory process in the media. Heller considered it a specific luetic condition. All of these authors agreed that the formation of aneurysms was associated with the replacement of these areas of injury in the elastica of the media by fibrous tissue. They considered that the scars offered less resistance to the pressure within the vessel, and consequently allowed aneurysms to form in these areas. This was the accepted view to which Benda has taken exception. He says that the conception that the elastica is responsible for the distensibility of the arteries particularly the aorta and that the replacement of the elastica by connective tissue increases the distensibility in these areas is not in harmony with other physiological and pathological experiences. The

*leimgebende Bindegewebs-fibrille* are practically non-elastic, as we encounter them in tendons and scars. He continues that while the media is elastic it is easily broken, but that the adventitia is neither elastic nor easily broken. The apparent elasticity of the adventitia is due to the fact that the connective tissue fibres when at rest are wrinkled. The toughness of the connective tissue of the adventitia is demonstrated in dissecting aneurysms where, having ruptured the media, the blood is held in by the adventitia. The resistance of the adventitial connective tissue hinders the overdistention of the elastica. A rupture of the elastic lamellæ is only possible when there is a preceding or concomitant destruction of the connective tissue fibers. Benda, therefore, concludes that the direct cause of every aneurysm lies in the inflammatory or traumatic destruction of the connective tissue either associated

and terminate with necrosis of the media and intima. In all probability the saccular dilatations occur at this time.

The following case confirms this view of Fabris and Benda.

Colored female, age 29 years. Autopsy No. 3565.

*Clinical History.*—The patient was a maid in the service of one of the attending physicians of this clinic. As far as could be ascertained she had been well until the present illness, with the exception of a fever, supposed to be malarial, during the summer of the past year. About two weeks before death she began to have headaches, but seemed well otherwise. She worked the entire day and was found dead in bed the following morning.

*Anatomical diagnosis:* Syphilitic aortitis with multiple small aneurysms one of which pressed upon and occluded the posterior coronary artery; coronary thrombosis below aneurysm; chronic pelvic peritonitis.

*Heart.*—The heart is normal in size and external appearance.



FIG. 1.

with or followed by the traumatic or dystrophic destruction of the elastica. He further states that if the above statements are accepted the medial scars in mesoarteritis are not to be considered in the formation of aneurysms. He admits, however, that their rigidity may bring about harmful results, inasmuch as their lack of elasticity may render them more likely to be the seat of traumatic aneurysm, though to a much less extent than the rigid calcified plaques occurring in endarteritis chronica deformans. Benda<sup>10</sup> believes with Etienne, Hertz, Babes, Puppe and others that the gummatous processes found in the arterial wall are the points of origin of the aneurysm. He agrees entirely with Fabris who came to the conclusion that aneurysms may develop in syphilitic aortitis, as soon as the granuloma has succeeded in destroying a sufficient portion of the arterial wall. These specific granulomata Fabris believes begin in the periadventitial connective tissue and in the adventitia from whence they gradually involve the media

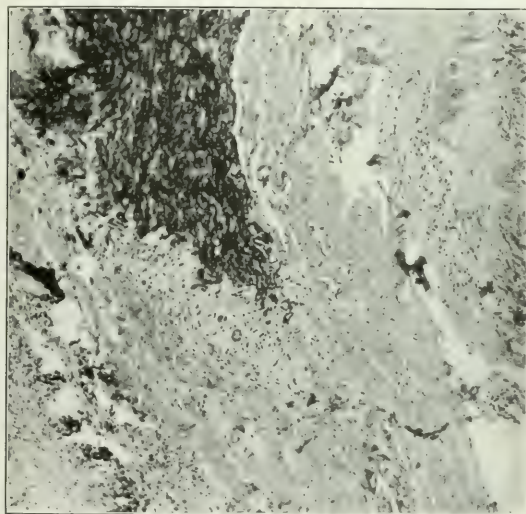


FIG. 2.

Its cavities and valves as well as the myocardium are unaffected. The base of the aorta shows a few small yellowish plaques, one of the larger ones being situated just at the mouth of the anterior coronary artery. Just above and to the left of the mouth of the posterior coronary artery there is a pouching of the aortic wall about 0.5 cm. in diameter. Projecting from the mouth of the posterior coronary artery is a recent small friable clot of a grayish yellow color. It is not adherent to the vessel wall and extends into the coronary artery for a distance of 1 cm. where the vessel is found to be in contact with the apex of the small aneurysmal sac above described. Around the mouth of the above sac the intima of the aorta is thickened, grayish in color and broken. On cutting through, the wall of the aorta may be seen to be thickened. This thickening is most marked in the adventitia, which is grayish in color and contains numerous small capillaries, distinguished by their bright red color. Several similar aneurysms though smaller may be seen at the origin of the aorta. Otherwise the vessel appears normal and quite elastic. The other organs show nothing of particular importance.

The microscopic findings are illustrated in the three accompanying figures. Figure 1 is a photomicrograph of the aneurysmal

sac. In the region of the sac the intima may be seen to be slightly thickened, but shows no tendency to undergo retrogressive metamorphosis. The sac is best outlined by the media which is particularly conspicuous since the elastic tissue has been specifically stained. The media may be seen to be quite irregular and at the apex of the aneurysmal sac it is considerably fragmented and invaded and replaced by a cellular granulation tissue. The adventitia is very markedly thickened. Figure 2, a higher magnification of the apex of the aneurysmal sac, shows the broken elastic tissue lamellæ surrounded by a granulation tissue. At the very apex of the pyramid formed by the elastic tissue fibers a miliary gumma composed of giant and epithelioid cells is found replacing the adventitia. Throughout the remaining portion of the adventitia there is a similar cellular infiltration. The third picture is simply a higher magnification of the miliary gumma at the apex of the pyramid formed by the broken media.

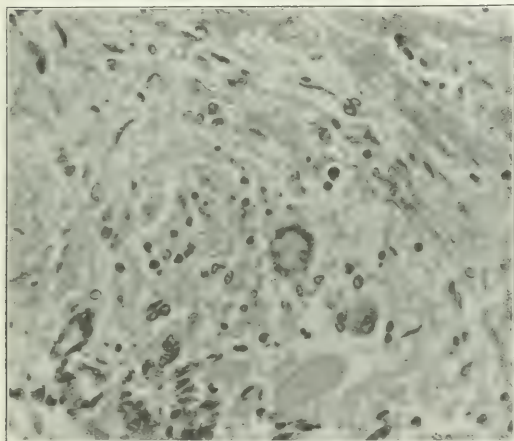


Fig. 3.

## CONCLUSIONS.

There is no evidence in favor of the view that the medial fibrosis occurring in aortitis is the source of the aneurysms occurring in this condition.

On the other hand the case report included in the above article shows an aneurysm in its incipency with the minute sac extending through the acutely broken and necrotic media to the adventitia where there is a specific granuloma present. This indicates that aneurysms of the aorta may form in the active stage of syphilis.

The adventitia shows the specific granulomatous process most characteristically. An extension of the inflammation

from the adventitia to the media no doubt plays an important rôle in the destruction of the medial fibres. In addition the rupture of the elastic lamellæ may depend in part upon the diminished support offered by the non-diseased adventitia.

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# AORTIC ANEURYSM RUPTURING INTO THE PULMONARY ARTERY, WITH A REPORT OF THREE CASES.

By HOLLAND NEWTON STEVENSON, M. D.

(From the Pathological Laboratory of The Johns Hopkins University.)

Aneurysms rupturing into the pulmonary artery are infrequent as is shown by the occurrence of only three in the post mortem records of The Johns Hopkins Hospital. One of these was encountered in a recent case, the other two were obtained from the autopsy records. In two of the cases the aneurysmal sac was large and had a free opening into the pulmonary artery. It is interesting to compare the physical signs of these two cases with those of the third case, which had a small sac and a recent pin-point perforation into the pulmonary artery.

Cases of thoracic aneurysm rupturing into blood vessels are not particularly infrequent, the usual sites being the inferior vena cava, the superior vena cava or the pulmonary artery. Osler states that those rupturing into the pulmonary artery are probably most frequent; those rupturing into the superior vena cava next in frequency; and those rupturing into the inferior vena cava least frequent. Among the 3900 autopsies at The Johns Hopkins Hospital, the three cases below reported are the only ones of perforation of a thoracic aneurysm into the pulmonary artery. In 1907 Kappis collected 32 cases from the literature of aortic aneurysm perforating into the pulmonary artery and reported a similar case. Three of these cases were complicated by rupture into the ventricle. He refers to other similar cases, reported without autopsy findings. The clinical features and physical signs of the cases presented are discussed at length. Since Kappis' publication, reports of individual cases of the same type have been made by Hollis in this country and by Lenoble and Chapel in France.

**CLINICAL HISTORY—CASE I.**—I. B., colored male, admitted to the service of Dr. L. F. Barker of The Johns Hopkins Hospital, September 19, 1912, complaining of shortness of breath. His family history is unimportant as is also his personal history, except that he has had several attacks of gonorrhea; he gives no history of syphilis. His present illness started about Christmas, 1911, with sudden shortness of breath which has continued and become aggravated. Associated with this there was precordial pain, swelling of the legs, abdomen, and extremities. During the latter part of his illness there have been severe coughing spells associated with considerable blood-stained sputum and nausea.

**Physical Examination.**—The patient is a well nourished colored man, sitting up in bed, resting on his arms. He has marked dyspnea and is apparently in great pain. The physical signs may be briefly summarized as follows: The veins of the neck are greatly dilated, and there is a whirling murmur over the subclavian arteries. There is no definite tracheal tug but a definite transmitted pulsation may be felt over the trachea.

**Thorax.**—The percussion note is impaired and almost flat over the right base and above the spine of the scapula on the left side with suppression of the breath sounds in these areas. There are numerous moist râles at both bases.

**Heart.**—The point of maximum impulse is not very definitely localized in the fifth interspace in the mammary line. There is a diffuse heave to the whole sternum. In the third interspace just above the nipple and along the left border of the heart there is a localized pulsation where a friction fremitus, synchronous with the heart beat, is felt. The relative cardiac dullness begins

at the second rib and extends  $1\frac{1}{2}$  cm. to the left in the 5th interspace, and  $5\frac{1}{2}$  cm. to the right in the 4th interspace. On auscultation at the apex a systolic blow accompanies the first sound which is loudest and most intense near the sternum. At the base and just to the left of the sternal border a diastolic murmur is heard. The pulmonary second sound is accentuated. In the area where the fremitus is palpable, on auscultation there is a machinery-like whirl, made up of a rough systolic murmur, an accentuated second sound and a blowing sound that runs through both diastole and systole. The pulse in the two radials is equal but definitely collapsing. There is a shifting dullness in the flanks. The extremities are markedly edematous, the tissue pitting with difficulty.

Death occurred rather suddenly on the second day after admission. The patient called for a sputum cup, expectorated a small amount of blood-streaked sputum, which was followed by pure blood. This gushed from his nose and mouth and ended in collapse and death within a few minutes (1100 cc. being collected).

Autopsy, No. 3779, was performed two hours after death.

**Anatomical diagnosis.**—Syphilitic mesaortitis; aneurysm of the transverse arch of the aorta communicating with the pulmonary artery; marked hypertrophy of the right ventricle; chronic passive congestion of the viscera; ascites; terminal rupture of aneurysm into left lower bronchus.

**Body** is that of a rather well nourished colored male. There is edema of the extremities and body wall. The abdominal cavity contains about 250 cc. of a clear fluid. The right pleural cavity contains 2 litres of blood-stained fluid and a few fibrous adhesions are present. The left pleura contains about 500 cc. of a similar fluid and numerous old fibrous adhesions. The pericardial sac has an excess of straw-colored fluid.

The heart is greatly enlarged and weighs 740 gms. with aorta and aneurysm. The right auricle is dilated and its wall is slightly hypertrophied. The tricuspid ring measures 14 cm., the valves being delicate. The right ventricle is greatly hypertrophied. The columnæ carneæ stand out prominently and the wall measures 9 mm. The pulmonary ring measures  $9\frac{1}{4}$  cm. The valves are delicate. The vessel wall shows nothing abnormal. The left auricle shows no definite changes. The mitral ring measures 11 cm. and the valves are everywhere delicate. The wall of the left ventricle is 16 mm. thick. The aortic ring measures 9 cm. The aortic valves show no change. The surface of the aorta is everywhere smooth and glistening except for a few, scattered, small, yellowish, opaque spots and streaks. The myocardium is apparently normal as are also the coronary vessels.

**Aneurysm.**—Opposite the orifice of the carotid artery and 8 cm. from the aortic ring, there is a large opening in the wall of the aorta 9 cm. in circumference which communicates with an aneurysmal sac. This sac arises from the anterior and in part from the inferior wall of the transverse arch of the aorta and extends inferiorly to the pulmonary artery which it overlaps; and anterio-laterally to the left, where it is adherent to the upper lobe of the lung. There are two communications between the sac and the pulmonary artery where they are in contact. The larger is round, and 1 cm. in diameter. It is on the anterior surface of the pulmonary artery  $5\frac{1}{4}$  cm. from the pulmonary ring. The smaller is oval 2 mm. by 1 mm. in size and is about 7 mm. above the larger communication.

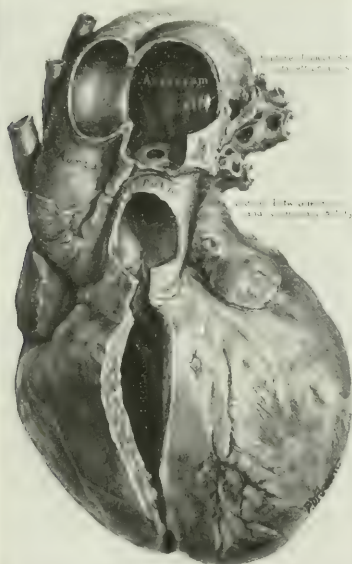
These orifices have well rounded and smooth edges. The lateral wall of the sac shows two more openings where it is adherent to the lung. The one about 1 cm. in diameter, opening into the primary bronchus to the lower lobe; the other, much smaller, opening into a secondary bronchus. The lining of the aneurysmal sac is rather corrugated and covered with a thin layer of fibrin.

*Lungs.*—The left upper lobe is collapsed and non-air containing. The lower lobe is dark purple in color and on section it is firm and of a homogeneous dark purple color. On opening the trachea it is filled with a recent clot.

The other organs show nothing of specific interest, being only typical examples of chronic passive congestion.

*CLINICAL HISTORY*.—CASE II.—J. S., white male, age 26, admitted to the clinic of Dr. L. F. Barker on January 10, 1910, complaining of pulsation of the heart. His family history is negative.

*Personal History.*—He has always been well. He has had no venereal disease, but admits frequent exposure. On December 4,



ANEURYSM OF CASE I.

1908 he was admitted to the hospital when the following clinical note was made: "Patient is well nourished but pale. The carotid pulsations are marked. The pulse is larger on the right than left and is a well marked, water-hammer pulse. There is distinct precordial fullness above and inside of nipple, which is most marked in the second interspace 5 cm. from the mid-sternal line. Retraction in the 4th and 5th interspaces. There is a visible and palpable rebound over the pulsating area. The lungs are negative on auscultation and percussion.

"*Heart.*—The point of maximum impulse is not definitely localized. The relative cardiac dullness extends to the left; 15 cm. in the 5th interspace; 13½ cm. in the 4th interspace; 14½ cm. in the 3d; and 14 cm. in the 2d. To the right it extends 4½ cm. in the 3d interspace. At the apex, and best in the 4th interspace just inside of the dullness, the first sound is sharp and followed by a short, snappy blow well heard in the back. In the axilla and back the first sound has a tapping character suggesting mitral stenosis. The second sound is barely audible at the border of

dullness, but as one approaches the mammillary line in the 4th interspace a distinct ringing second sound with a peculiar echoing quality is heard. In the 3d interspace there is a continuous machinery murmur with systolic accentuation. A very slight second sound is audible.

"In the 2d left interspace, in the midst of the general echo a distinct to and fro diastolic murmur is audible and a well marked second sound close to the sternum. In the aortic area a diastolic murmur is heard along the left border of the sternum. The to and fro murmur is heard associated with the second pulmonic. To the right of the sternum a blowing systolic murmur with a sighing quality is well audible. The second sound is rather sharp. The heart is fixed in position."

On December 18, 1908, the aneurysm was wired by Dr. J. M. T. Finney, following which the patient's condition became improved and he was discharged in June, 1909. In November of the same year he caught cold and suffered much pain in his chest on coughing.

Four weeks before his final admission he became puffy under the eyes. He had many vomiting spells and much shortness of breath. When admitted, January 10, 1910, the following clinical note was made:

The patient is sitting up in bed by preference, resting on his arms. He shows some loss of weight, his lips and ears are cyanotic, and the mucous membranes are pale. The vessels of the neck are full, being more so on the right. In the carotids there is a systolic thrill and on auscultation a continuous hum with systolic accentuation is heard. The pulse is collapsing, that on the left being smaller than the right. A definite tracheal tug is felt. There is a diffuse heave of the chest with systole and there is a marked pulsating prominence above the left precordium. The lungs are clear, except for impairment at both bases.

*Heart.*—The point of maximum impulse is 14½ cm. to the left in the 5th interspace and rather indefinite. There is slight systolic retraction of the lower part of the thorax. The expansile impulse is localized in the 1st, 2d, 3d and 4th interspaces where a continuous thrill with systolic accentuation is felt. The relative cardiac dullness is continuous with the pulsating mass and extends to the left; 16 cm. in the 5th interspace, 12½ cm. in the 3d, 11½ in the 2d, and 10½ in the 1st interspace. It extends 5 cm. to the right in the 4th interspace. At the apex, the sounds are feeble and a very loud systolic murmur is heard, which is well transmitted, and an equally rough diastolic murmur. These are maximal along the left border of the sternum. At the base the second pulmonic is loud, snappy, and accentuated. Over the pulsating area a continuous rough murmur is heard having a systolic accentuation. Both sounds are heard here but the second sound is very loud, snappy and accentuated. These sounds and murmurs are heard all over the right front and left back. There is dullness in the flanks and edema of the extremities.

The patient died on January 11 after numerous coughing and vomiting spells having gradually become weaker.

Autopsy, No. 3323, performed January 11.

*Anatomical diagnosis.*—Syphilitic aortitis; aneurysm of the ascending arch of the aorta; erosion with opening into the pulmonary artery; compression of vessels and bronchi at the hilum; chronic adhesive pericarditis; cardiac dilatation and hypertrophy; chronic passive congestion of the viscera.

*Body* is that of a well nourished white man with cyanosis and puffing of the face. The liver extends 11 cm. below the costal margin in the mammary line. There is a large amount of fluid in the right pleural cavity. The pericardial sac is obliterated. On the anterior mediastinum is found a mass composed of two portions. The upper is a large spherical mass, 10 cm. in diameter, which gives on palpation the sensation of a thin sac in the wall of which are thin pieces of shell. Beneath this is felt a muscular organ. The former mass is firmly adherent to the parietal wall.

*Aorta*.—From the bifurcation up to the arch, the aorta shows only a few scattered atheromatous patches. The arch is normal as is its ascending portion along its posterior surface, but on its anterior and left surface, about 6 cm. from the aortic ring, is a great dilatation of the vessel, having a definitely circumscribed mouth, formed by a ridge of elevated yellowish tissue which is of a firm cartilaginous consistency. This opening occupies the concave and anterior portion of the ascending arch, commencing 1 cm. from the aortic valves. The sac extending from this opening is large and contains a recent clot, collected around silver wire. The wall is irregular and corrugated, being covered, especially opposite the orifice, with laminated clot, but being thin in some places and having areas of calcium deposits. The sac presses the pulmonary artery to the left and posteriorly, and the wall of this vessel has become thinned, and there is a hole in it 6 mm. in diameter, 1 cm. above the pulmonary orifice.

*Heart*.—The right auricle is dilated and its wall thinned where it was in contact with the aneurysm. The tricuspid ring measures 15 cm. in circumference. The valves are delicate and apparently competent. The right ventricle is dilated and its wall thickened, measuring in thickness almost 1 cm. The pulmonary valves are delicate. The left auricle is not extremely dilated and its appendix is fixed in position by adhesions. The mitral ring measures 11½ cm. The valves are delicate. The ventricle on this side shows a thickened wall which averages 8 mm. but is 22 mm. in its thickest part. The aortic valves are slightly thickened and do not seem to be exactly competent. The heart muscle shows only a few translucent streaks of fibrous tissue.

The other organs show chiefly chronic passive congestion.

**CLINICAL HISTORY**.—CASE III.—O. W., colored male, age 45, was admitted to the clinic of Dr. William Osler on January 5, 1892, complaining of shortness of breath and weakness of the legs. From the family history it seems that several members suffered from heart disease. Personal history is negative. Present illness began in October, 1891, with a cold and cough. Four weeks before admission shortness of breath set in with occasional attacks of nausea and vomiting. He could not sleep lying down. His legs and ankles have been swollen only the past few days. There has been some nicturia and some expectoration.

*Physical Examination*.—Patient is a well nourished man suffering from shortness of breath. He has pale mucous membranes. The pulse is regular but of low tension. The resonance of the chest is good except for flatness at the right base with distant breath sounds in this area.

*Heart*.—Impulse 2 cm. outside nipple line. Dullness begins at the upper border of the third rib and extends to the right border of the sternum and through the nipple to the apex impulse. No thrill is felt at the apex. On auscultation at the apex the first sound is faint, the second sound is replaced by a dull, prolonged thrill. As one passes upwards a dull murmur becomes more audible, the diastolic being louder and more accentuated on the 3d rib. Three finger's breadth from the sternal margin the second pulmonary is sharply accentuated through the murmur over the base. Approaching the sternum in the 3d interspace the murmurs are heard at their loudest, the diastolic having a somewhat musical character. In the aortic area a double murmur only is heard. A single murmur of moderate intensity is present in the carotid. Abdomen is rather full. There is edema of the extremities. The patient improved for a short time under rest and treatment, but finally grew weaker and died on January 11, 1892.

Autopsy, No. 267, was performed on January 12.

*Anatomical diagnosis*.—Aneurysm of aorta; hypertrophy and dilatation of heart; chronic passive congestion of lungs; and abdominal organs; pin-point perforation from aneurysm into pulmonary artery.

*Body* is that of a large, strongly-built man, with large and turgid veins of the neck. The peritoneum, right pleura and pericardium contain an excess of fluid.

*Heart* weighs 450 gms. The aortic valves appear normal and the aorta is smooth throughout. There is an aneurysmal opening 2½ cm. long near the opening of the left coronary artery, which extends as an aneurysmal sac downwards and backwards along the edge of the valve into the ventricle. The wall of the sac is smooth, but has some pit-like depressions, the deepest of which extends into the sinus of the middle cusp of the pulmonary artery. The projection into the latter is about 2 mm. high; to which prominence the cusp is partly adherent. At the tip of the prominence is a small projection into the pulmonary artery of fresh fibrinous vegetations. At this point is the opening from the aneurysmal sac into the pulmonary artery, which is about 0.5 mm. in diameter. The aortic ring measures 7 cm. The mitral ring measures 11 cm. The myocardium of the left ventricle is 16 mm. thick. The tricuspid ring measures 12 cm. The myocardium of the right ventricle is 6 mm. in thickness. The other organs are typical examples of chronic passive congestion.

*Summary*.—1. The points of clinical differentiation between the cases with a large communicating opening into the pulmonary artery (Cases 1 and 2) may be contrasted with those of the third case, which presented only a tiny opening, and summarized as follows:

(a) Enlargement of the heart to the right (Cases 1 and 2). No enlargement to the right (Case 3).

(b) A continuous thrill and murmur in the carotid and subclavian (Cases 1 and 2). A single murmur and thrill (Case 3).

(c) In the third left interspace (Case 1) a continuous murmur with an overlying rough, systolic murmur.

Case 2 had a continuous murmur with a systolic accentuation. Case 3 had a systolic and diastolic murmur.

(d) Cases 1 and 2 had a collapsing pulse. Case 3 did not.

2. The origin of the aneurysms was as follows: Case 1, from the transverse arch, in Cases 2 and 3 from the ascending arch of the aorta. The points of perforation into the pulmonary artery were in Cases 1 and 2 on the anterior surface of the artery 5¼ cm. and 1 cm. from the ring respectively. In Case 3 the perforation took place on the posterior wall behind the posterior cusp of the pulmonary valve.

3. That the pulmonary perforation had been present for a relatively long period of time in Cases 1 and 2, is borne out by the immense hypertrophy of the right ventricle, which is not evident in Case 3. The lack of change in the physical signs in Case 2 over a period from 1908 to 1910 also upholds this point.

4. In Case 3 the perforation, although recent, had no bearing on the death of the patient, while in the other two cases it had existed for so long a time that the conclusion can be drawn that perforation of an aneurysm into the pulmonary artery is not incompatible with life.

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ALLERGY AND RE-INFECTION IN TUBERCULOSIS.<sup>1</sup>

BY EDWARD R. BALDWIN, M. D., Saranac Lake, N. Y.

It will be noted that my subject as announced in your program presumes to a degree upon the knowledge of newly-coined terms by the audience. Although Prof. v. Pirquet's sojourn here was short, I am sure his admirable studies in the field of hypersensitiveness, or "changed reactions," are well known and appreciated. Since he first applied the word "allergy" to the phenomena of "changed reactions," as a general term, without wishing to convey any theory of its nature, immunology has made further advances. The many manifestations of allergy have been studied exhaustively both in tuberculosis and other diseases, with the result that it is safe to range it under the head of immunity or protective functions. I used the term advisedly in my title to avoid a more complicated descriptive one, and to have no reason to explain it. I would also urge its general use.

A year ago when the subject of immunity to re-infection was brought more prominently into tuberculosis literature by Prof. Paul H. Roemer, one of the foremost German workers, but little interest was excited by it, judging from the lack of discussion on the part of the tuberculosis clinicians in Europe. Fortunately to my thinking, Drs. Hamman and Wolman have shown a thorough appreciation of its importance in their recent excellent work on "Tuberculin in Diagnosis and Treatment." More recently Col. G. E. Bushnell, of the Army Medical Corps at Fort Bayard, has also reviewed Roemer's and Hamburger's experiments and deductions as to primary and secondary infection.<sup>2</sup> The far-reaching import of these deductions warrants abundant study in both laboratory and clinic. Therefore, if some of my remarks seem like needless repetition of facts already familiar to you, I hope you may find enough angles of view to repay you for listening. I venture now to present some observations intended for your meeting on this date last year, when illness interfered with my attendance.

It has seemed to me that we have not generally appreciated the important bearing some of the earlier experimental work on tuberculosis in this country has on the problem of infection. We have become so accustomed to the current exaggerations about the danger from infection to adults as well as children, that we have overlooked strong proofs to the contrary. If we can now marshal facts, both experimental and clinical, to disprove some of the popular teaching in reference to infection, I believe a great service can be done for the prevention of cruelty to consumptives. It ought to allay fears of contagion to some extent at least, and there is a duty for public authorities in this connection.

For the sake of clearness, I shall define at the outset my understanding of the word "allergy" as applied to tuberculosis. It should include all forms of tuberculin reactions, whether local or general, or any inflammatory process caused

by tubercle bacilli or their products after infection has been established. It should then be a very comprehensive term, covering practically all manifestations of the reactions between the tissues and the disease agent.

It is well established that after primary infection, it requires 10 to 15 days to develop the allergic state. Up to that time the infection has aroused but little response in virgin soil. Then follows an inflammatory stage, fever develops, and local changes announce the fact that tubercle bacilli have called forth a specific change. Henceforth the individual responds differently to a subsequent exposure. The minute studies of v. Pirquet are so familiar that it is unnecessary to review them. The course of tuberculin skin reactions abundantly demonstrates the principle, and it is of course schematic for many other forms of allergy. What I wish to refer to in particular is the intimate nature of the reaction and its apparently protective function as related to re-infection in tuberculosis.

*Nature of Tuberculin Reaction.*—As is generally accepted at present, tuberculin reactions are evidences of tuberculo-protein hypersensitiveness. My associate, Dr. Krause, presented before this society two years ago a review of our work at the Saranac Laboratory on this subject. He has since extended it with interesting results, some of which bear on the problem of re-infection and will be referred to later. There has been a tendency to doubt the propriety of considering the tuberculin reaction as closely related to other forms of foreign protein sensitiveness. This was mainly due to the inability to sensitize normal animals with tuberculin and elicit anaphylactic death or symptoms similar to those produced by other proteins in sensitized animals. In some of my earlier work the results were negative or inconclusive, but later we succeeded in obtaining positive anaphylaxis with crude tuberculin, or a similar glycerine extract of the bacilli, as well as with the pure protein extracts.

On the other hand, there are features of the tuberculin reaction not closely paralleled by other protein-sensitive reactions. There are the focal and cutaneous reactions, the auto-tuberculin effects excited by hyperemia of a tuberculous focus and also those produced in highly sensitive tuberculous subjects by heterologous proteins, such as beef albumose or other bacterial proteins.

Through the complete correspondence that we have found to exist between the anaphylactic reactions of tuberculo-protein and those of other proteins, we have felt that here the key to all the reactive phenomena of tuberculosis should be found. This is doubtless true but not easily demonstrated. The problem of creating skin sensitiveness, for example, without producing a tuberculous focus in an animal has engaged my attention for some years.<sup>3</sup> Thus far I have not succeeded either by the use of the tuberculo-protein alone or mixed with the various waxy substances extracted from tubercle bacilli. The bearing of this

<sup>1</sup> Paper read before The Laennec, a society for the study of tuberculosis, The Johns Hopkins Hospital, April 28, 1913.

<sup>2</sup> *The Military Surgeon*, January, 1913.

<sup>3</sup> Studies from the Saranac Laboratory, 1900-1904, 1904-1910.

point on the subject in hand will perhaps be more apparent later. Now, with many other proteins it is quite possible to create a specific skin sensitiveness, *e. g.*, beef serum, but it seems to require the presence of actual tubercles in the animal before cutaneous reactions to the old tuberculin or the pure protein extracts can be elicited. A collection of powdered animal charcoal saturated with tuberculo-protein and placed under the skin or in the peritoneal cavity as a depot or storehouse has failed in my hands to create skin sensitiveness. The addition of the fatty substance extracted by benzol was also unsuccessful.<sup>4</sup> Similar experiments were made independently by Stocker, an assistant of Prof. Sahli, and are mentioned in the last edition (3d) of Sahli's Tuberculin Treatment (1912). He employed Beranek's tuberculin in an insoluble precipitate, but without success in creating sensitiveness.

Thus far I have referred to sensitization with filtered extracts of the tubercle bacilli as a means of sensitization. When intact, dead bacilli are injected in sufficient numbers, skin sensitiveness appears and disappears with the formation and absorption of the tubercles thus formed (as you know, tubercle formation is readily produced by either dead or living bacilli), hence the inference that the tubercles are essential to this reaction. Further, it might be supposed that intact bacilli were also essential. This is apparently possible also, though experiments in sensitization with pulverized bacilli have shown slight skin reactivity.<sup>5</sup> In these, however, the presence of a few intact bacilli and the formation of temporary tuberculous tissue were not excluded. The same criticism may be made of the attempts of Much & Loeschke<sup>6</sup> to create tuberculin reactivity with bacilli dissolved by lactic acid, neurin, and other solvents. Tuberculous foci are often too minute to be discovered by the most careful post mortem examination, and I am compelled to think that all experiments in immunity against tuberculosis where the tuberculin fever and skin reactivity have been established, can be explained in this way. I refer to the bovo-vaccination of v. Behring and Roemer, Koch, Heymanns and v. Baumgarten, as well as the earlier experiments of Trudeau, and Pearson and Gilliland in this country. Not only the tuberculin reactivity but the immunity acquired by the animals is explained by the presence of tuberculous foci produced by the vaccine. It is true the tubercles are not always discoverable nor are they necessarily permanent lesions when the vaccine used is of low virulence, yet it has been found that the best relative immunity thus obtained persists no longer than the allergic state of the animal, or in other words, until the complete disappearance of the vaccine or obliteration of the foci caused by it.

We are brought to the conclusion that the immunity acquired by vaccinated animals rests upon the presence of tuberculous tissue. Roemer<sup>7</sup> is not sure of the identity of the allergic reaction to re-inoculation with the reaction to tuberculin, be-

cause the latter may be absent in animals who show a marked hypersensitiveness to a new infection. Moreover, he calls attention to the fact that by treatment with dead bacilli tuberculin allergy can be produced, yet no perceptible immunity developed. While the reason for these differences in reaction is not easy to explain, I think it is a mistake to think that the mechanism is at all different. One suggestion is that the dose of tuberculin or bacilli used, as well as the manner of administering it, may govern the result of a test in a vaccinated animal, whether positive or negative. It is too much to assert this, but allowing for varying degrees of susceptibility there is much to support it. It is quite true that calves and rabbits may lose all reacting power to moderate doses of tuberculin after vaccination, and yet when re-inoculated respond with a sharp allergic reaction. The absence of tuberculin allergy in these cases is probably more apparent than real, only the dose may not be large enough to arouse fever. I do not know of intravenous tuberculin tests being made in such animals. The sum of all our observations is that relative immunity in tuberculosis is associated with the allergic state, either active or latent, and this passes away gradually with the disappearance of the primary vaccination or infection.

There is, nevertheless, one allergic reaction that may never be wholly lost during life, once sensitization has occurred. This is the capacity for anaphylactic shock, and it seems to persist quite irrespective of the focal and febrile reactions. Neither does an animal show any perceptible immunity from experimental infection if only sensitive to anaphylactic shock (Krause<sup>8</sup>). Possibly the limitations of experiments on guinea pigs may account for the negative results, but certainly a high degree of immunity can be induced in these animals by inoculations of bacilli attenuated in virulence and which lead to a delicate allergic sensitization.

It is natural to enquire into this difference and its cause. I have no theory to offer except to again call attention to the importance of the focus containing the bacilli as contrasted with the sensitization with soluble products of the bacilli, possibly altered by the simplest manipulations so as to lose some element of importance. More than likely the difference is merely in degree. The focus is to be considered as a collection of cells more highly "trained" (if one may use an athletic term) to react, because in continuous contact with the bacilli. It is less easy to account for the tissues being sensitized that are not in direct contact with the bacilli. These are suggestive fields for experiment.

From what has been said it is implied that any actual infection with tubercle bacilli produces a certain amount of protection against subsequent infection; at least while the allergic state persists.

*Super- and Re-Infection.*—It will be well here to distinguish between "super-infection," or "additional" infection, which predicates the existence of active or latent disease, and "re-infection," occurring after clinical healing of a pre-existing

<sup>4</sup> Investigations into the Nature of Tuberculin Sensitiveness, Transactions of the Seventh Annual Meeting National Association Study and Prevention of Tuberculosis, 1911.

<sup>5</sup> Studies from the Saranac Laboratory, 1904-1910.

<sup>6</sup> Much & Loeschke: Beiträge z. Klinik d. Tuberk. XX, 409.

<sup>7</sup> Beiträge z. Klinik. d. Tuberk. XI, 130.

<sup>8</sup> Studies from Saranac Laboratory, Jour. Med. Research, 1911, XXIV, 361.

tuberculosis. In making such distinctions it must be remembered that there can be no hard and fast line drawn between clinical healing and latency. In both cases tuberculin allergy persists so long that this test cannot be used as a criterion of healing in the human subject. In the bovine race the same holds good in relation to natural infection. The real problem is to determine whether this allergy is dependent on the extent of the original infection, its incomplete healing, or upon a true re-infection, whether from outside sources or from auto-reinfection. It is well known that an encapsulated tubercle of small extent, and to all appearances healed in the clinical sense, may yet be the only discoverable source of a positive tuberculin reaction. It is also true that the delicacy of the reaction is usually in inverse proportion to the age and in direct proportion to the extent of the healed focus. In many persons in adult life this is probably the reason for the delayed or feeble response to the cutaneous tests, as v. Pirquet and Wolff-Eisner have explained. It requires repeated subcutaneous or even intravenous tests to make certain that some degree of allergy is not present. This is, however, of little practical importance. What we wish to know is, how much value the primary infection is to us as a protection, and if the allergy is always a desirable condition. The experiments of Koch, Trudeau, De Schweinitz, v. Behring, and many others on guinea pigs, rabbits, cattle and sheep clearly showed, when interpreted in the present aspect, that it was a protection. The more recent ones of Nichols\* in our laboratory can now be interpreted in the same light.

It is to Roemer and Hamburger that we are chiefly indebted for bringing forward direct experiments bearing on super-infection and also to Wolff-Eisner for emphasizing the principle. The first two workers showed that it was practically impossible to produce a second infection in guinea pigs already diseased with chronic tuberculosis. Roemer has tried intracutaneous, subcutaneous, inhalation and feeding methods in attempts at super-infection, and from these and all the preceding experiments of v. Behring and himself on vaccination against tuberculosis, he finds further confirmation of v. Behring's ideas of infection in early life and the relative immunity which follows a mild infection. He finds the course of the disease in adults and the types seen in different races to be best explained on the basis of these experiments. Without going into all the points of epidemiology and the question of paramount importance, the proportion of infections in early life, which Roemer considers at length, I desire to touch only the aspect of re-infection or, as it must be in many cases, super-infection. At the start it is to be remembered that the immunity above mentioned is only relative, not absolute, and yet it may be very effective. We know that the bodily resistance is fluctuating and dependent upon numerous factors. In animal experiments with tuberculosis we cannot imitate or parallel all the human conditions, so we are obliged to infer from clinical evidence that resistance to tuberculosis varies widely at times and is frequently broken down. It is harder yet to discover that a new development of the disease is a re-infection from outside when an autogenous source is easily possible.

We are obviously confronted by many puzzling possibilities. For convenience, we may divide the population into four classes: *First*, those who never have received a tuberculous infection and hence do not react to tuberculin. They are mostly under the age of ten. *Second*, those who have received a very slight infection, in quantity, virulence or both. This includes a large number of healthy adults who may or may not react to tuberculin. *Third*, those who received an infection sufficient to produce symptoms of disease, either latent or progressive. Many of this class will be found in tuberculous families. They will usually react strongly to tuberculin. *Fourth*, those who received a primary virulent infection progressive and fatal.

We shall readily see that many of the first class will become infected as they grow older, until practically all will sooner or later react to tuberculin. Next we shall have to assume in the light of the experimental observations that all the infected classes acquired some specific immunity at the time of their infection. In the last two classes one can hardly expect a superinfection from outside sources, knowing the much greater probability of auto-infection. The agencies that would make for reduced resistance to exogenous infection would also encourage autogenous super-infection.

The greater second class is the one most liable to exogenous re-infection, and the great majority of them must be exposed from time to time to it. While they are in good health and continue to show tuberculin allergy, it is very likely that they will resist exogenous infection by inhalation or swallowing. If inoculation accidentally occurs as in many pathological students, or purposely as F. Klemperer and C. Spengler have done on themselves, we know that the infection remains localized usually in the skin or nearby glands. The bacilli do not die, or at least not all of them, and even in Roemer's and Hamburger's experiments were found to be virulent, though apparently restrained from further growth.

It is of interest to know what would happen to an individual who has apparently lost the tuberculin allergy in the lapse of time, and while in good health inhales tubercle bacilli. We have no answer to this from the experimental side, except in bovine vaccination, yet we can pretty surely predict that no infection will take place in the majority. As soon as the bacilli shall obtain lodgment in the tissues, the old allergy will quickly return and localize if not destroy them.

*Anergy.*—We must go further and enquire what will be likely to happen to individuals who have lost tuberculin allergy from disease, as is known to occur in measles and scarlatina. I refer to the observations of v. Pirquet and others where no response occurs to the tuberculin cutaneous test during the height of the disease. Here again it was found to return after convalescence and could hardly fail to act in the event of exogenous infection. Outbreaks of tuberculosis during convalescence from other diseases are not easily associated with recent infection in the sense that exogenous bacilli were implanted during or after the illness. More often, as we know, the bacilli were already present in the lymph glands or old nodules from a previous infection. During the condition of "anergy," as ex-

\* Nichols, J. L.: The Medical News, 1905, LXXXVII, 641, 653.



plained by v. Pirquet, the bacilli may be scattered and create new foci when allergy returns. Of course we are in danger of taking a too narrow view of infection if this is our only explanation of the mechanism. Undoubtedly, the hyperemia around the glands at the root of the lung furnishes mechanical conditions of great importance in certain diseases like measles and influenza. Here we have a tuberculin-like focal reaction at an unfavorable time. With it doubtless there may be a loss of protective functions, such as digesting ferments, antibodies, and leucocyte activities, such, if you please, as opsonins. I think we should class all those which act specifically against tubercle bacilli as "ergins" in possibly a broader sense than the word is used by v. Pirquet. This would not prejudice any theory as to the relative importance of the specific substances, but it has the advantage of comprehending all of them.

When the allergic state is restored, we should expect a different pathologic picture in the spreading tuberculosis than in a primary infection. This is in fact the case according to many observations. The marked infiltrations in the lungs, pneumonic consolidations in reality, are accounted for by the strong allergic reaction. The contrast between these and miliary tubercles is very evident, and can be demonstrated experimentally (Nichols<sup>10</sup>). The development of a strong allergy in previously infected individuals is at least one reason why miliary tuberculosis is not more frequent during relapses and extensions of the disease. The recent discovery of bacilli in the circulating blood, more frequently than formerly thought possible, adds to the belief that some powerful protection exists to overcome them. This has been especially noted by v. Behring and Roemer.

That miliary tuberculosis is accompanied by anergy has been proven by v. Pirquet. Acute pneumonic tuberculosis also leads to this state when cachexia develops, but the lesions undoubtedly antedate the failure of reactive power. Weakened allergy occurs after tuberculin treatment, but this is not necessarily a sign of weakened resistance, nor is reaction power wholly lost; it is only in abeyance as shown by occasional high fever reactions when the dose of tuberculin is increased enough. Wolff-Eisner,<sup>11</sup> however, argues that this tuberculin treatment anergy is favorable to further infection.

Having found so many ways in which the bodily resistance is broken down and tuberculosis develops, we would enquire whether simple overwork, worry, underfeeding, injuries, and the like are accompanied by anergy. If so, will it permit exogenous infection? I do not know of any studies on the tuberculin reaction from this point of view. In large series of tests, like those of Beck<sup>12</sup> and Franz,<sup>13</sup> it is hardly probable, as least, that the large percentage of positive-reacting individuals were all in good condition when tested. It is also certain that many persons in very bad physical condition, who suffer from overstrain as well as latent tuberculosis, react strongly to tuberculin. Moreover, it is certain that the disease often spreads under these

conditions from the primary source. To account for this, it has been thought by some that auto-infection was more dangerous than exogenous, because the bacilli were adapted, as it were, to the individual. Roemer's<sup>14</sup> attempts to reinoculate guinea pigs with their own bacilli, however, were not successful by way of the skin, although the original disease was progressive. Finally, it has been shown, especially by Hamburger, that the super-infections tend to ulceration—if the dose be sufficient—at the site of injection. In natural infections, however, the exogenous bacilli are generally inhaled or swallowed, or both; and the question arises whether they can penetrate the allergic individual under any circumstances. I think it was Prof. Theobald Smith<sup>15</sup> who first suggested the possible cause of cavitation in the lungs to be the inhalation of bacilli of higher virulence than the first infection, which were held at the portal of entry, but were able to produce local damage. While this is one explanation, cavitation is often seen in animals with a long-standing chronic tuberculosis in which no question of secondary exogenous infection can be raised. Without facts to favor a theory of re-infection of a formerly allergic person, we can only admit that possibility. If possible at all, the conditions are likely to be extreme in number and virulence of bacilli.

On the other hand, there are some reasons to consider the lung parenchyma, especially in the apices, a place of lower resistance to tubercle bacilli than other external surfaces. If this is true, inhaled bacilli in adults are conceivably lodged in the alveoli, and as in Hamburger's experiments, may grow and produce surface ulceration in an allergic individual. It appears to be a field not satisfactorily covered by investigation. Super-infection with ulceration in the lungs is demonstrable, but according to all the experimental evidence it is autogenous.

What we most wish to know for the peace of mind of the public is under what conditions, if any, exogenous super- or re-infection occurs in the pulmonary area. The clinical literature of inoculation tuberculosis of the skin and mucosa is not very satisfactory in furnishing evidence of re-infection of the lungs. The surfaces are certainly all exposed but not to be compared. Furthermore, autogenous infection of the lungs is clearly the most common form from all experimental evidence as well as pathologic studies.

Most of the writers on tuberculosis have recognized the astonishing infrequency of laryngeal and intestinal super-infection in open tuberculosis. This refers of course to the individuals who still have good vitality, or, translated into the terminology here employed, efficient allergy. As the disease advances naturally a change takes place and the allergy reveals its paradoxical action; it is so exaggerated that harm results from the toxemia and ulceration. Here we have one rationale for tuberculin treatment, about which much dispute has arisen. It seems reasonable to attempt to lessen the high sensitiveness seen in many patients and in the scrofulous children particularly. I cannot follow Wolff-Eisner<sup>16</sup> in his belief that abolition of tuberculin skin and fever reaction leads to danger of

<sup>10</sup> *Loc. cit.*

<sup>11</sup> Frühdiagnose u. Tuberkulose Immunität, A. Wolff-Eisner, 1909.

<sup>12</sup> Deutsche med. Wchnschr., 1899, Vol. XXV, p. 137.

<sup>13</sup> Wien. klin. Wchnschr., 1909, Vol. XXII, p. 991.

<sup>14</sup> Beiträge z. Klinik d. Tuberk. XVII, 316.

<sup>15</sup> Theobald Smith, J. Am. M. Ass. 1906, XLVI, 1253-4.

<sup>16</sup> *Loc. cit.*

further infection. The further we study these reactions the more they appear to be life-conserving rather than health-conserving. While we seem to be protected in ordinary exposure against a fatal miliary tuberculosis, tuberculous patients are slowly poisoned by the very mechanism of resistance overdeveloped or over-active. I do not press this point too far, or is it settled beyond doubt? It is enough to draw attention to the double-edged action of allergy.

In conclusion it seems pertinent to make some practical use of our knowledge of allergy in tuberculosis. If some things sound too speculative, and my deductions are pivoted on too small points, yet we are reasonably sure of some things. These are (a) that most adults have received some tuberculous infection; (b) that a variable degree of specific allergy is thus acquired; (c) that during ordinary health the tissues repel tubercle bacilli, partly with the aid of specific allergy; (d) re-infection is mostly autogenous super-infection and due to disease, overstrain, trauma, or any cause of lowered vitality, whatever that may mean. Finally, (e) as a corollary, adults are very little endangered by close contact with open tuberculosis, and not at all in ordinary association. Childhood is the time of infection, youth the time of super-infection, and that from extension of the primary disease.

Qualify these statements as we may, it is time for a reaction against the extreme ideas of infection now prevailing. There has been too much read into the popular literature by health boards and lectures that has no sound basis in facts, and it

needs to be dropped out or revised. More protection of children and better hygiene for adults are logically demanded, but beyond this the preachments about the danger of infection to adults in the present state of society are without justification from an experimental standpoint. Deductions from case histories must be accepted with much doubt, when circumstantial evidence is presented showing the source of infection to be recent exposure in adult life.<sup>11</sup> This is particularly applicable to the question of hospital and dispensary contact for nurses and resident staffs. It also applies to alleged infection of married partners, already the subject of careful investigation, without producing satisfactory proof of infection (Weinberg,<sup>12</sup> Pope and Pearson<sup>13</sup>).

Phthisiophobia has had no check from the time the knowledge of the bacillus was popularized. Cornet's dust experiments first gave the impulse, to a fear, followed by Flügge's droplet infection, which has aggravated the solicitude felt by physicians and nurses and which has been gradually spread to the laity. Not until the researches that I have briefly laid before you have we had much to show the way to a more correct judgment of the real danger to adults.

<sup>11</sup> Bruck and Steinberg (Ztschr. f. Hyg. u. Infectiousk., 1912, LXXI, 177) conclude that 31 per cent of cases studied by them were classed as such. They admit the lack of proof.

<sup>12</sup> Beiträge z. Klinik d. Tuberk. 1906, v.

<sup>13</sup> Draper's Company Research Memoirs III, 1908.

## PROCEEDINGS OF SOCIETIES.

### THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

*February 17, 1913.*

Dr. Thomas S. Cullen presiding.

**Myelogenous Leukæmia treated by Benzol.** DR. L. F. BARKER and DR. J. H. GIBBS.

This gentleman, a private ward patient who is kind enough to come down here to-night, is 57 years of age. He entered the hospital November 23, complaining of nervousness and general debility. The family history is negative.

In March, 1906, he was treated in this hospital for neurasthenia and left the hospital comparatively well. He continued to feel well until two months before his present admission, when he began to have feelings of general insufficiency. On physical examination no abnormalities were found. He was referred to one of us by Dr. Randolph of Charlottesville, Va., on account of the marked increase in the leucocytes of his blood. Examination showed a red blood cell count of 3,600,000; white blood cells 360,000; hemoglobin 79 per cent; the stained smears and differential count yielded a typical picture of myelogenous leukæmia. The spleen was not palpable. The Wassermann reaction was positive. X-ray of the long bones was negative. The urine contained hyaline casts, and a small amount of Bence Jones body (Dr. Guthrie).

The results of treatment with a new method (benzol) have

been so remarkable that we felt that the patient should be seen by the members of this society.

The method of treatment used during his stay in the hospital was as follows:

From November 24 to 26, no treatment was given. On November 26 Fowler's solution, beginning with 3 minims and increasing, was ordered. On November 26, 1912, the white count was 250,000, and on December 5, 1912, 192,000. After five days a single dose of neosalvarsan was given, and on December 10, 1912, the count was 210,000. Benzol was now begun and the Fowler solution stopped.

The origin of the benzol treatment is of interest. You may recall that some three years ago, three girls who had been poisoned by benzol in a factory in Baltimore, entered the medical clinic of this hospital for observation and treatment. They had been severely poisoned and developed anæmia and purpura hemorrhagica, two of the cases ending fatally. Dr. Selling, who studied the tissues in Professor Welch's laboratory, found an extensive aplasia of the bone marrow of these patients. Since Dr. Selling's studies, considerable experimental work has been done in the pathological laboratory here by Dr. Winternitz and his associates. It is interesting that the therapeutic application of benzol grew out of the studies of Dr. Selling. Professor von Korányi, in Budapest, noticed the studies of Dr. Selling and thought it might be well to try benzol in the

treatment of leukaemia. The effects were remarkable. He has kindly sent us reprints of his articles and we have used the method in treating this patient, with good results.

We have seen that on December 10, before benzol was started, the white cell count was 210,000. After five days of benzol, that is on December 15, the count was 184,000; this represents relatively little change, not more than had been taking place before the administration of benzol. On December 25, the count was 170,500—very little diminution. It was Professor von Korányi's experience that in the first three weeks of benzol treatment, very little change in the white count is observable. On January 25, the count was 98,000—a definite drop. On January 30, it had fallen to 48,000 and on February 13, to 14,200. The hemoglobin, as you see, is 71 per cent now, contrasted with the 65 per cent shown when he came in. Benzol, in suitable doses, seems to stimulate the erythropoietic marrow while it reduces the leukopoietic marrow. We have stopped the benzol now because it has been observed that the diminution in the number of the white cells goes on after benzol is stopped and we do not desire to cause too much hypoplasia of the marrow. The differential counts of the white cells in the course of the treatment are interesting and will be given in detail when the case is reported in full. The results obtained with this patient make us feel sure that there will soon be a general interest in the treatment of leukaemia by benzol. It is, of course, far too soon to pass judgment upon the real value of the treatment.

The substance should be most cautiously employed to avoid benzol poisoning. It would probably be wise to limit its use at present to hospitals in which close watch can be kept over the patient's condition. Dr. Frank Billings, of Chicago, has recently reported several cases treated with benzol, and several articles on the subject have already appeared in European literature.

**The Statistical Experience Data of The Johns Hopkins Hospital, 1892-1911.\*** FREDERICK L. HOFFMAN, Statistician, The Prudential Insurance Company of America, Newark, N. J.

#### DISCUSSION.

DR. H. M. HURD: I am sorry that Mr. Hoffman has not seen the tables which were prepared many years ago in connection with the Michigan State Hospital for the Insane at Kalamazoo.

I became connected with that institution in 1870, and one of my first occupations was to tabulate what had happened to one thousand selected insane patients. Tables were prepared containing the names, ages, forms of insanity and the termination of treatment in these cases, that is whether they had recovered, improved, died or were remaining in the institution. The form of tabulation proved so instructive that in 1872 it was adopted as a form for statistics, and for a number of years, at least as long as I remained connected with the institution, these tabulations were used.

\* To appear in full as a monograph of The Johns Hopkins Hospital Reports.

When I removed in 1878 to Pontiac, Michigan, where I opened the Eastern State Hospital, I adopted the same form of tables and published them annually until 1889, when I removed to Baltimore. Here the question of statistics soon after opening the institution again came up, and after consultation with Drs. Welch and Billings, it was decided to adopt the form of table which had already been used in Michigan.

It was thought best in view of the varying morbidity and mortality of the white and colored races to make separate tabulations for them, a casual study of the health statistics of the city of Baltimore having shown the death rate among the white patients to be about 20 per cent, and that of the colored race about 33 per cent.

I did not then fully realize the value of these tabulations because I was not a statistician, but I hoped that some good would come out of it. These tables have been continued for nearly 24 years, and I am gratified that at last all appreciate the advantages which may come from their use.

As to the dispensary tables, I can only say that there are some difficulties in connection with dispensary work, owing to the fact that many patients only come to the clinics once or twice and if the disease is at all obscure, it is difficult and well-nigh impossible for a conscientious medical man under the circumstances to make a definite diagnosis. For this reason in many services the list of forms of diseases has been imperfectly filled out and under the heading "Unascertained" a large number have been classed. I hope that with better methods in the dispensary and an increased amount of medical assistance it may be possible to improve the character of the dispensary statistics.

DR. L. F. BARKER: Dr. Osler is always urging that we appoint a thoroughly trained statistician to the hospital, and I hope that this meeting to-night may stir us up to make arrangements for a first-class man to work here all the time. It was gratifying indeed to hear such an appreciative statement as Mr. Hoffman has made regarding the statistics as kept thus far. I was much interested to see how clearly he had put his finger on certain peculiarities of our work, merely from his study of these statistics; it is certainly striking that a man from outside, who has no actual knowledge of our local conditions, should be able, by his consideration of the statistics alone, to pick them out. Local conditions should, of course, always be kept in mind in attempting to interpret the significance of statistics. For instance, in drawing deductions regarding the relative number of admissions for race and sex one should know the whole number of beds provided for white men and white women in each service, and the number for colored men and colored women, or he might be seriously misled. Again one should know how many "pay" and how many "free" patients there are. Again, the duration of the hospital stay varies greatly for patients suffering from different diseases. The relatively small number of cases of certain diseases treated in this hospital may throw no light on incidence, but be due to lack of provision for, or of special interest in them. For instance, the small number of "tuberculosis" admissions was pointed



out. Thus, patients suffering from outspoken pulmonary tuberculosis are not admitted here; only occasionally a case slips in unrecognized until after admission. The hospital is used mainly for the treatment of acute, rather than of chronic, diseases. If chronic cases are admitted, it is usually for a brief period of observation and diagnosis rather than for prolonged treatment. That alters the whole statistical picture. This feature is well illustrated in comparing surgical with medical admissions. A surgical ward is largely an institution for therapy, but a medical ward has to be, at present, to a large extent, an institution for diagnosis; and this influences the statistical results very definitely.

The speaker had a good deal to say about the "morbidity" of a large city like Baltimore. Regarding this, inferences should be drawn only with great caution from our statistics. Consider just one point: the colored wards draw chiefly from the city, the white wards chiefly from outside of the city. The public wards for white patients and the private wards of this hospital draw from the country at large, and so any statistical deductions regarding morbidity in the city would be fallacious unless this fact was especially considered in the tabulations.

Similarly, the comparison of the mortality rate of white and colored people for a given disease might seem to be fair in a hospital in which the colored people are treated and studied just as carefully as the white people; but, nevertheless the conditions are different for the two races. The colored people do not come into the hospital until they are absolutely compelled to and often cannot get in unless they are very seriously ill, whereas more white people can enter as pay or part pay patients, and thus enter for milder maladies than do the colored. Anyone who knows wards M. and O (the colored wards) has been struck by the number of patients suffering from aneurysm and from cardiovascular diseases. Many of them enter shortly before "exitus"; for humanitarian reasons it is necessary for us to care for them, while many of our white people with similar diseases can be well cared for in their homes. Again, while Wassermann reactions are common in both the colored and the white wards, still the proportion of positive to negative reactions is much higher in the former than in the latter. If our statistics indicate as they do that the mortality among the colored men entering the hospital is much higher than that among the white men, we must remember that a whole series of conditions have to be considered in order properly to interpret the fact. It is instances like these which emphasize the importance of a statistician constantly working in the hospital, and familiar with all the peculiarities of our local conditions.

Take another example to which Mr. Hoffman referred: the mortality statistics for malignant diseases among white men and white women. When the mortality statistics in men and women suffering from malignant disease are quoted, very different groups of diseases are under comparison. "Malignant disease" in men is very different from "malignant disease" in women. If you analyze the surgical diagnoses of malignant disease in women you will probably find that they consist, in large part, of cases of carcinoma of the breast, of the uterus, and of the stomach. In men, a similar analysis will probably

reveal predominantly cases of carcinoma of the lip, tongue, œsophagus, stomach and rectum. I am speaking wholly from impression but I am very sure that the incidence of malignant diseases in men and women would be very different for the several organs, so that in comparative statistics, unless one choose a given malignant disease of a given organ rather than merely malignant diseases as a whole, deductions are sure to be fallacious.

I say these things, not at all in criticism of anything that Mr. Hoffman has said, but simply to emphasize the great importance of a full knowledge of local conditions for the proper keeping and valuation of hospital statistics. Each of us connected with the hospital must always be grateful for the great service Mr. Hoffman has rendered us in these careful studies of his and for pointing to the way we should follow.

DR. W. H. SMITH: I don't think I have anything particular to add to what has been said. It is always interesting to note the free and easy manner in which recommendations are made for the appointment of additional workers. I wish it were as easy to find the money with which to pay for them.

While Mr. Hoffman was speaking of the great value of statistics, it was brought to my mind that in the last few years the question of hospital statistics has more than once been up for discussion in the meetings of the American Hospital Association. The authorities of some hospitals have maintained that the statistics published in the annual reports were useless and might well be eliminated. Some hospitals have discontinued publishing such statistics. From what Mr. Hoffman has said it is possibly just as well that they have done so. If I understood him correctly the published statistics in the majority of hospital reports are of very little value. It is an interesting and remarkable fact that practically no two hospitals use the same terminology in tabulating their statistics relating to diseases. There is no uniform nomenclature. In this hospital some work has been done by Dr. McCrae and others, but it has never been satisfactorily completed. I happen to have been a member of a committee of the American Hospital Association which reported at the last annual meeting on the subject of uniform nomenclature for hospital publications. The committee, after conference with various authorities, among others Mr. Cressy L. Wilbur of Washington, recommended the adoption of the Bellevue Hospital nomenclature. The most extensive work along this line has apparently been done by the Committee of Records at Bellevue. Dr. Warren Coleman and Dr. Robert Carlisle have been the chief workers. They have worked for the last eight or ten years in bringing out a small volume known as the Bellevue Hospital Nomenclature. It has been revised two or three times, the last revision having appeared about two years ago. At that time their work had been brought into conformity with the International Classification of Causes of Death, and in it appeared for the first time a very valuable classification of industrial diseases.

There is still much work to be done along this line. I mention this, because many of you here will be going out to other hospitals in various parts of the country and will have your

opportunity to contribute something to the better development of hospital statistics.

DR. F. L. HOFFMAN: I am glad indeed that some additional points have been raised in discussion which, on account of the limitations of time, could not be included in my address. As regards resident and non-resident patients, it is unfortunate that this distinction should not appear in the annual reports, but it would obviously be a most difficult matter to fully account, in all the required details, for the admissions and mortality by the residence of the patients. I may say in this connection that there is a table included in my address which shows that in proportion to population the number of deaths in Baltimore hospitals, according to residence, was as follows: resident whites, 16.7; non-resident whites, 7.0; resident colored, 32.6; and non-resident colored, 8.3. These rates are per 10,000 of population, and they would hardly sustain the point raised that a much larger proportion of non-resident whites are treated in Baltimore hospitals than non-resident colored.

As regards the duration of treatment, I regret that there is no information contained in the annual reports other than a table giving the average duration for all causes, which is stated to be 22 days. This table I have included in the Statistical Appendix to my address, together with some financial data as regards the cost of treatment.

Concerning the details of cancer by organs or parts of the body affected, I regret that for want of time I could not enter into a full discussion in the course of my remarks, but in the addresses as it will subsequently be published every form of cancer is given in detail, together with the death rate, whether medical, surgical, or gynecological, so that every combination of facts can be made as desired. If I had gone into the details of cancer mortality there would have been no end to this discussion, but all the facts are contained in the Statistical Appendix to my address.

I have been particularly pleased with what has been said by the former superintendent of Bellevue Hospital, and I sincerely hope that the Bellevue classification of diseases will hereafter be used by the Johns Hopkins Hospital, instead of the present and more or less antiquated and misleading one. It is much on account of the cumbersome classification that I have not been able to complete my analysis by diseases, since quite frequently the same diseases are reported under different terms. The classification used does not admit of comparison with others, and if you want to aid in the effort to bring about uniformity in nomenclature you cannot do better than to adopt the Bellevue classification.

What has been said with reference to the tendency on the part of hospitals to eliminate from their annual reports the desired statistical account of the hospital experience, I cannot but feel is most regrettable. I, however, am inclined to think that if hospitals do not of their own account publish full returns concerning their experience, sooner or later the government will insist upon a full accounting for what is unquestionably a most important public function. In this respect the demand will not be for less but for much more information, just as there is

an increasing demand for publicity on the part of corporations and other business concerns. In any event, Johns Hopkins Hospital stands in the front rank of publishing annually the kind of reports which should be made public by all American hospitals, regardless of size or class of patients treated, whether public or private, and I sincerely hope that my address will aid in bringing about this much to be desired result.

March 3, 1913.

Dr. Thomas S. Cullen presiding.

**The Treatment of Syphilis of the Nervous System with Especial Reference to Tabes Dorsalis.** DR. ARTHUR ELLIS, Rockefeller Institute, New York.

#### DISCUSSION.

DR. L. G. ROUNTREE: In listening to the papers of Drs. Ellis and Keidel I have been tremendously impressed with the close analogy existing between syphilis and trypanosomiasis, more especially in regard to their failure to respond perfectly to treatment. In trypanosomiasis the same four possibilities as to the reasons for failure of treatment, *e. g.*, relapse, have to be considered, *viz.*, *festigkeit*, difference in individual resistance, inaccessibility of the organism to medication and the possibility of a life cycle in some stage of which the organism resists the action of drugs. *Festigkeit* is not the primary cause of relapse, since this cannot play a rôle until several treatments have been administered, and relapse occurs after the first treatment just as it does after the twentieth. Also, relapses in trypanosomiasis occur after treatment with sodium antimony thioglycollate toward which *festigkeit* could not be demonstrated.

There are probably other areas of the body beside the cerebro-spinal canal and central nervous system which serve as sheltering or protecting areas during drug therapy. The bone marrow extracts of treated trypanosome animals give frequent successful inoculations when extracts from many other tissues fail.

Terry has recently shown that incubation of atoxyl serum at certain temperatures increases its toxicity for trypanosomes. The explanation of this fact is not yet apparent.

DR. H. M. THOMAS: I have listened to the paper of Dr. Ellis with extreme interest. I have been so fortunate as to have had the opportunity, when visiting the Rockefeller Institute from time to time, of seeing Dr. Ellis and Dr. Swift at work, and I have been impressed, as I am sure every one must have been, by their skill and accuracy. The tables that Dr. Ellis has shown us in themselves demonstrate this.

As he was speaking I could not help thinking of the various stages of development through which our knowledge of the relationship between syphilis and tabes had passed during my own interest in diseases of the nervous system—now more years than I care to recall. At the beginning of this time Fournier in Paris, Erb in Heidelberg, and Gowers in London, had just called attention to the probable causal relationship between syphilis and tabes—a view that at that time was quite novel. One of the chief criticisms of this view by its opponents was

that anti-syphilitic treatment appeared to have no result on the development of tabes; indeed, the idea was advanced by some that tabes was actually caused by the effects of mercury on the spinal cord. However, ever since the hospital was opened all our cases of tabes have been consistently and thoroughly treated by the anti-syphilitic methods in use at the time, with what result, of course, it is difficult to say, but we have seen a number of cases in which the process has remained practically stationary during many years, and in some cases remarkable improvement has occurred. Anyone who has had much experience with the treatment of tabes knows how hard it is to estimate from the mere clinical phenomena what has been accomplished, and it will be the greatest boon if it turns out, as seems probable, that the laboratory study of the spinal fluid does give us reliable data. I should like to ask Dr. Ellis what is the longest time that the spinal fluid has remained normal in his cases.

**DR. J. T. GERAGHTY:** Whatever may be the explanation for the failure of salvarsan to cure syphilis, there are several practical points which our experience with the drug during the last few years has brought out.

In the first place, the importance of seeing and treating patients in the early stage should be emphasized. It is our experience, as well as that of others, that those who present themselves in the primary stage, with a chancre only, and a negative Wassermann, can be completely and permanently cured by one or two injections. In the secondary stage, repeated injections of salvarsan combined with a vigorous course of mercury, should be employed. The amount of treatment necessary will have to be judged from past experiences, as well as from observations upon the blood. Quite a few of these patients with early or late secondary syphilis receiving repeated injections of salvarsan combined with intramuscular injections of mercury, have been under observation sufficiently long to believe that they have been cured. In the latent and long-standing cases the results with the salvarsan therapy have been most disappointing. It is extremely doubtful if salvarsan can completely cure a larger per cent of the cases in this class than were formerly cured by mercury.

**DR. A. G. RYTINA:** The work of Drs. Ellis and Swift opens a new and important field in syphilis therapy. Those of us who treat many cases of syphilis by salvarsan, know that the chances of a radical cure thereby depends largely on the time that we carry out radical treatment after the onset of the infection. The reason for the many failures of salvarsan in the later stages of syphilis is not due to any lack of specificity of the drug for the spirochæta pallida, but may be explained by the pathologico-anatomical changes present in syphilis after it has lasted some time. In chronic syphilis the spirochæta become deposited in the form of encapsulated rests and often in parts of the body inaccessible to the circulation. Following salvarsan administrations, the vast majority of the spirochæta are destroyed, but the few escaping may later on generate a new progeny and be responsible for recurrence of symptoms, etc.

It has been shown by Weichselmann that the cerebrospinal

fluid may show a positive Wassermann reaction even before the onset of secondaries and while the blood is still negative. Now the work of Ellis and Swift and others has shown that the ordinary drugs, used in the treatment of syphilis, such as mercury, potassium iodide and salvarsan, are not excreted at all, or only in very minimal amounts in the cerebrospinal fluid.

It has occurred to me that if a routine examination were to be made of the cerebrospinal fluid, as well as the blood, in all cases of suspected lues, and if those individuals presenting a positive Wassermann in the cerebrospinal fluid were given the direct intraspinal treatment, as well as the general treatment now employed, it would be possible to greatly lessen the percentage of parasyphilis cases, as well as cause a larger number of permanent and radical cures. Is it not possible that the spirochæta, when they get in the cerebrospinal system, are free from therapeutic attack, and not only capable of setting up lesions of cerebrospinal syphilis, but of sending their progeny to other parts of the body to cause future recurrences, etc. This is all theory and may be worth very little.

I would like to emphasize the point brought out by Dr. Geraghty, viz., the necessity of seeing these cases early and putting them upon prompt and vigorous treatment. I try to impress upon my students the importance of an early diagnosis by the demonstration of the spirochæta pallida and the need of instituting vigorous treatment, before the onset of secondaries, or the appearance of a positive Wassermann reaction. In the last few months I have administered neosalvarsan in 12 to 24 cases of primary syphilis by the multiple injection method. None of these patients have developed secondaries, and in all the Wassermann reaction is negative. How long this state will persist time alone will tell. I feel, however, that the future will prove that the majority of them have been cured.

**DR. A. ELLIS:** We have not had an opportunity of observing over any length of time cases whose spinal fluid has been reduced to normal. The spinal fluid of one patient has remained normal without any treatment for about four months. Whether these cases will remain normal or not is impossible to say, but probably some at least of them will relapse. In case such relapse occurs, they should, of course, have further treatment.

We have seen no indication of progress of optic atrophy in any of the patients under treatment. Several patients who have had a well-marked atrophy have had repeated intravenous and intraspinal injections. In most of these cases the color fields and visual fields have been repeatedly tested and in no case has any material alteration occurred.

Dr. Keidel has spoken about the variation of individual susceptibility. This variation plays an important part, I think, in the treatment of syphilis. One patient whom we have seen illustrates this very well.

This patient was treated from the beginning of the secondary eruption, with repeated injections of salvarsan and mercury. During the first year of his treatment he had 6 gm. of salvarsan and many intramuscular injections of mercury. At no time was he without treatment for longer than four weeks. In spite



of this, he had three clinical relapses. At the end of a year, on account of symptoms suggesting a possible meningitis, he was lumbar punctured and his spinal fluid showed 212 cells, a positive globulin reaction, and a positive Wassermann reaction. His treatment was then changed to neosalvarsan, and under this he rapidly improved and has now had a normal spinal fluid and a negative reaction of the blood for a period of four months.

In this patient neosalvarsan has seemed more efficient than the old salvarsan. This is in marked contradistinction to our general experience where we have found the old salvarsan very much more efficient. There is, apparently, an individual variation.

March 14, 1913.

Dr. Thomas S. Cullen presiding.

**The Cultivation of the Virus of Epidemic Poliomyelitis.** DR. SIMON FLEXNER AND DR. HIDEYO NOGUCHI, Rockefeller Institute, New York.

**The Presence of Treponema Pallidum on the Brain of General Paresis.** DR. HIDEYO NOGUCHI.

#### DISCUSSION.

DR. ADOLF MEYER: It is not difficult to get one's enthusiasm stirred over a meeting of this kind. In a field like psychiatry where such a large variety of conditions confront one, it is a great comfort to feel that 15 per cent of these cases that we have to consider present problems which can be approached more and more definitely through the test tube, and that real helps in such investigations have been brought to us to-night. Psychiatry can be proud in this, that even with its apparently crude methods it has been able to single out of the supposedly confused mass of conditions such a clearly defined group and to assign it to the field of syphilis before even the spirochæta was known. I cannot help being reminded of an impression of one of my former associates, who had been an assistant in one of the largest hospitals in the country and who had watched with great interest the anatomical service of that hospital. He had come to feel that in general hospital work the anatomist was the one man who could have positively solid evidence under his feet, while the clinician was so frequently humiliated at the autopsy table with the shortcomings of his diagnostic means. In charge of the autopsies in our hospital for the insane he was strongly impressed by the fact that where the diagnosis of general paresis had been made clinically it was with surprising uniformity that the characteristic autopsy findings were established and the clinical diagnosis was substantiated by the post mortem studies. And that was before Wassermann came to our help. It was this field of psychiatry that freed him of a deeply rooted nihilism about the scientific strength of ante mortem pathology. From a neurological and in a great many instances the psychopathological point of view, it was possible to single out from among the many other forms of dementia the conditions which at the autopsy of the brain showed the cloudy oedematous pia and the adhesions to the cor-

tex, the granulation of the ventricles and the infiltration of the cortical vessels with lymphoid and plasma cells, and which gave us the means of making a remarkably well-defined anatomico-clinical entity of parenchymatous syphilis. This most interesting observation of Dr. Noguchi distinctly opens to us an avenue of study which also was foreshadowed clinically, viz., the study of the question of why it is that in these conditions this widely present organism behaves in such a highly different way from what it does in other tissues of the body. It may also become possible to learn why it is that of 9 glass blowers infected from one source 5 developed locomotor ataxia or paresis, i. e., what we called metasyphilis, or what we now should call parenchymatous syphilis, and whether it is possible to demonstrate a different strain of spirochæta in the cases yielding "metasyphilis." It will now become possible to demonstrate the actual type of spirochæta present in the cerebrum and spinal cord. It will also become possible to try the findings of the Rockefeller Hospital where very successful efforts have been made in tubes to bring the therapeutic agents closer to the spirochæta through the cerebrospinal fluid. So far, general paresis has looked to us as a condition which can only be attacked by a vigorous onslaught against the spreading of syphilis in general. I have no doubt that that will remain the most important prophylaxis against general paresis proper, but where infections have occurred we are given at least some chance of obtaining, after experimentation, an accurate therapeutic means of attack. If we can hope to apply to the brain what has been already very successfully applied to the spinal cord in tubes, it does look as if some more direct means has been given us than the admittedly futile one of using potassium iodide and mercury products with these patients, or the highly empirical treatment with nucleo-proteid fever. It does seem as if now we could look forward to experimental work on some more direct attack on the spirochæta. I feel that Dr. Noguchi has opened a great field of research and moreover he has demonstrated what I would like especially to bring to the attention of the younger workers, he has shown that it is possible to do much good work in a special field like psychiatry even if one should not expect to devote himself permanently to the whole field of psychiatry. It is possible to single out lines of more or less limited work with excellent opportunities for valuable contributions. I hope that many will be as successful as Dr. Noguchi.

DR. J. HOWLAND: As members of the Johns Hopkins Hospital and Medical School, we are grateful to Dr. Flexner for telling us of the brilliant results that he and his co-workers have accomplished. But as physicians, present and prospective, we owe him a debt which we owe to few other men for information concerning one of the most dreaded and disfiguring of diseases. He has taught us much in regard to the propagation of poliomyelitis, much in regard to its pathology and he has indicated to a certain extent how we may avoid it, but he holds out the hope that no one else has held, that we may perhaps prevent and even eventually cure this scourge, for scourge it is. May I, therefore, Dr. Flexner, on behalf of all of us, express to you our very great gratitude and admiration!

DR. H. M. THOMAS: I may perhaps be permitted to second Dr. Howland's remarks from the neurological point of view, even though the studies at the Rockefeller Institute and elsewhere have transferred poliomyelitis from a strictly nervous disease to one of the general infections, under which heading it is now considered in Osler's Practice. However, as its manifestations are largely nervous, its study falls within my department, and ever since Dr. Flexner and his associates have been announcing at short intervals their many discoveries in regard to it, it has been, I think, the most interesting subject of the course. They have told us much, but there is much left to be made clear, but now that it seems certain that the virus itself has been isolated and cultivated, we await with admiration and confidence still more advance in our knowledge of the disease.

DR. L. F. BARKER: It is a great pity that Prof. Wilhelm Erb, of Heidelberg, cannot be here on this occasion. He has always maintained that tabes dorsalis and dementia paralytica are true syphilitic diseases, and Dr. H. M. Thomas, our neurologist here, has always held the same view. I am told that when Professor Erb heard of Dr. Noguchi's discovery he threw up his hands and said, "Hurrah, hurrah, the proof has at last been brought." Would also that the late Professor Rudolph Virchow could be here. He had always assented to the idea that lues might be responsible, but he insisted that the proof had never been brought. To say that one disease is due to some disease which preceded simply because of this precedence is no very valuable proof. Virchow pointed out that while tabes and general paresis follow lues, they also follow a common cold, for no patient with tabes or general paresis has a history of freedom from common colds! Virchow was right, of course, in pointing to the danger of fallacy; but the clinical evidence in favor of the luetic origin of the two diseases was strong. Could he be here, to-night, he would, I believe, also throw up his hands and rejoice at this demonstration.

America may well feel proud that this finding of the treponema pallidum in the cerebral cortex in general paresis has been made in this country. Of all contributions to knowledge bearing upon psychiatry thus far made in America, it may reasonably be asserted that this one made by Dr. Noguchi is the most important. It is interesting to note that this discovery has not been made by a psychiatrist, but by a man working in a pathological laboratory, one relatively unfamiliar perhaps with the facts of clinical psychiatry. The discovery is of fundamental importance, though, of course, as Dr. Noguchi has said, it does not solve the whole problem, even on the etiological side, though it does open up the way for further research.

The work which was done by clinicians long before the causal micro-organisms of syphilis was known and long before the Wassermann test was devised was really very wonderful. The clinical recognition of a whole series of different types of lues—primary, secondary, and tertiary, and of the paralytic diseases

is what I have in mind. It is the establishment of such syndromes by clinicians that gives the stimulus to laboratory workers for their researches. The fact, now definitely established, that the virus of syphilis is present in the cerebral tissue of paralytics does not conflict with the clinical fact that dementia paralytica differs from ordinary cerebral lues. We must still believe that "parasyphilis" differs from "tertiary" syphilis; and we have still to explain the differences. Why does lues affect the cerebrum sometimes in one way, sometimes in another? Are the parasyphilitic diseases due to the arrival of the treponema in areas beyond the blood vessels and the meninges, that is to say, in the tissues of the brain itself? Is it possible that "ordinary" cerebrospinal lues is predominantly an arterial or a meningeal localization of the treponemal injury, and that dementia paralytica and tabes are evidences of predominantly intraneural localization? May we not hope that the demonstration of this peculiar localization of the treponema may lead to a more satisfactory therapy in the paralytic processes? We have now to find out how to get salvarsan and mercury into spirillocidal relations with the parasites in these relatively inaccessible areas. We have long known that mercury, applied in the ordinary way, though it may help a paralytic patient, too often fails to arrest the disease; we have had the same experience with arsenic. The stimulating paper read the other night at this Society describing the work of Swift and Ellis on the treatment of paralues excites the hope that a new therapy is being devised that will be far more efficacious than any hitherto available. And it is interesting that the route chosen for the application here is the same as that utilized by Dr. Flexner for the introduction of the curative serum in epidemic cerebrospinal meningitis.

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*The Modern Hospital. Its Inspiration: Its Architecture: Its Equipment: Its Operation.* By John Allen Hornsby, M.D., and Richard E. Schmidt, Architect. With 207 illustrations. 1913. 8vo. 644 pages. W. B. Saunders Company, Philadelphia and London.

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# BULLETIN

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## CARCINOMA OF THE CERVIX OF THE UTERUS.

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AND

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*(Report from the Gynecological Clinic of The Johns Hopkins Hospital.)*

Although the radical abdominal operation for patients suffering from carcinoma of the cervix of the uterus was advocated as early as 1895 by Rumpf,<sup>1</sup> Clark<sup>2</sup> and Ries,<sup>3</sup> and in 1900 by Wertheim,<sup>4</sup> its general adoption has been surprisingly slow, and there are, even at the present time, energetic antagonists. If such a procedure is to have a place in fighting such an otherwise hopeless malady, its efficiency can best be determined by the occasional "checking up" of the ultimate results in patients so treated.

In Cullen's<sup>5</sup> comprehensive monograph, the cases of cancer of the uterus operated upon in this clinic by the various methods, until April, 1899, were reviewed, and, so far as possible, the post-operative results were accurately determined. Since January, 1900, a more or less uniformly extensive abdominal operation has been employed in practically all operative cases, and the results herein given are based upon such cases extending over the period from January, 1900, until January, 1912. The operations were performed by Dr. Kelly, his associates and the resident gynecologists of The Johns Hopkins Hospital.

In many of the early cases of the disease, it is impossible to make an absolute diagnosis without a microscopical examination. In order not to submit any patient to such an extensive operation unnecessarily the positive diagnosis should be made in every case. This is best done by making frozen sections of the mucosa or portion of the cervix as suggested by Dr. Cullen<sup>6</sup> in 1895. As stated by him, "This rapid method is of great importance in those cases in which it is not desirable to administer an anæsthetic twice, as the patient can come to the

operating room prepared for hysterectomy, which can be proceeded with as soon as the affirmative diagnosis is made. After curetting, the usual preparations will be made, and by the time they are completed the scrapings have been examined and the report is given. If carcinoma is present, the organ is removed at once; if, however, the examination is negative, the patient is returned to the ward, and is saved the suspense of awaiting for days to know whether she is suffering from malignant trouble or not."

*Anæsthesia.*—Complete relaxation is absolutely essential for a thorough dissection of the pelvic structures. In the majority of cases ether has been the anæsthetic employed, which is given by the open drop-method. In a few cases nitrous oxide, oxygen and a very small amount of ether have been given, which if competently administered approach most nearly the ideal anæsthetic in the majority of surgical operations. It is true, in the first place, that while the anæsthetic is being given, the patient is at her worst, and if necessary, the effects of the anæsthetic can be raised within a very few minutes; and in the second place the liability of post-operative pneumonia is greatly lessened. This form of anæsthetic is of especial value and is generally employed where there is any pulmonary complication or decreased renal function.

However, the choice of an anæsthetic must depend both upon the patient and the anæsthetist, since nitrous oxide poorly given is much inferior to ether moderately well administered.

*Operation.*—On account of the peculiar anatomical structure of the pelvic viscera, the extensive abdominal operation



must remain one of the most difficult surgical procedures, and the primary mortality will doubtless continue high even in the hands of the most skilled operators. As pointed out by Clark: "If an operation or other therapeutic procedure is to have a permanent place in our armamentarium, it must be sufficiently easy to make it available, not for a few skilled specialists, but for the great body of surgeons working in every quarter of this and other countries. In these days of low primary mortality percentages attending nearly all the major operations, no operation can possibly gain extensive headway which carries with it a shockingly high mortality, and a large number of distressing and disabling sequelæ." It is not an operation that can be properly performed after two or three trials, but will always require the best surgical judgment and technique if it is to be followed by any degree of success. It is the immediate result that impresses the minds of the laity, and this effect is not to be counterbalanced by an occasional cure. Since the average surgeon sees but a few cases even in a decade, it can scarcely become universally popular, but will be practically limited to the larger clinics.

Although the original operation still remains the same in its fundamental principles—the wide excision of the uterus with the parametria and the surrounding lymph structures "en masse"—from time to time various modifications have been adopted in order to render the technique more perfect and to lessen the time necessary for its completion. Since metastases usually occur late in the progress of the disease, the radical operation is theoretically well founded; aside from the early recognition of the existing condition, possibly the greatest hope lies in the technical improvement of this operation whereby the high mortality will be lowered and the operation made suitable even to the average surgeon.

From 1900 to 1903, 13 cases were treated by atypical operations. Since the object of this review is to determine the ultimate value of the extensive abdominal operation, these cases are not included in the various summaries of percentages.

*Operability.*—Since carcinoma is for a considerable period a local disease, the progress at first being by direct extension in the majority of cases, the mobility of the cervix is the determining factor as to whether or not the radical operation is to be done. Judged by this standard in the series of cases reported by Cullen\* from 1893 to 1899, the percentage of operability was 51.7. During the last seven years, 167 cases of carcinoma of the cervix of the uterus have been admitted to this clinic. Two cases refused operation. Out of 165 the radical abdominal operation was done in 95 cases, thus giving a percentage of operability of 57.2. In a way, such a high percentage of operability is misleading, as it does not represent the number in which there was any hope of absolute cure. Many of these cases were far advanced, and might have been sent away even by the most conscientious surgeon, but at their request the radical operation was done to relieve the symptoms.

Great efforts are being devoted to the developing of the operative technique, but unfortunately, its successful employment is tremendously handicapped by the failure in America to recognize the early symptoms. The usual history given by

these patients is that they have suffered from irregular bleeding from seven to nine months, and have been submitted to various treatments.

In many cases the limitation of mobility of the cervix and induration are due to an inflammatory reaction surrounding the carcinomatous area, which renders the prognosis more hopeful. Case 16152 is a remarkable example of just such a condition. This patient was admitted to the ward, and the diagnosis of inoperable carcinoma of the cervix was made. A thorough cauterization was done simply as a palliative measure. Twelve days later when the patient was examined before being discharged from the ward, the cavernous cervical growth was found to have diminished greatly in size and to have become quite freely moveable. The radical abdominal operation was done, and her convalescence was uneventful. Her physician writes, March 24, 1913, three years and four months after operation: Mrs. J. is apparently in perfect health. She has grown very stout and does a great deal of hard work.

*Radium.*—While analyzing our cases of cancer of the uterus treated by the radical abdominal extirpation method, we have been more and more impressed with the distressing number of women who apply too late for relief. And not only is the large group distressing in which it is impossible to operate, but still more discouraging are those upon whom we operate and who then soon suffer from a recurrence. It is in this series of cases that radium used in large quantities (100 to 200 milligrams at a time) offers the definite hope of adding to the percentage of "permanently cured" cases.

Radium can be applied "in tube" in the following manner:

1. It is applied to the disease with a view to curing it without any operation. An instance of this kind has been reported by Chéron. The patient, dying later of another disease, was carefully examined, and the cancer found to have been completely eradicated.

2. Radium is used to irradiate the disease thoroughly before the operation with a view to rendering innocuous any small foci of disseminated cancerous cells which may not have been extirpated and which would inevitably bring about a speedy recurrence.

3. Radium is inserted at the end of an operation:

- (a) To wipe out any cancerous cells left at the base of the broad ligament.

- (b) In cases in which, relying upon the radium to destroy them, the operation has been conducted deliberately through diseased structures.

4. One of the most precious uses of radium is in early recurrences at the vaginal vault, or laterally out in the broad ligaments, to wipe out the disease.

The field of usefulness for radium is not limited by these radical measures, but it is also serviceable, even where it does not cure, in restraining the disease, in checking the secretions, and above all in relieving the often distressing pains.

*Primary Mortality.*—The high primary mortality has been the most discouraging feature in the employment of such an extensive operation. From the above table we find the total primary mortality to be 20.4 per cent, while for the last five

## PRIMARY MORTALITY.

Genee. No.	Serial No.	Time of death.	Cause.
8689	7	3d day.	Very advanced case; patient rapidly weakened; pulse became rapid, irregular and weak; never became rational; surgical shock.
9092	15	4th day.	Advanced case; time of operation 2 hrs. 55 min.; autopsy No. 1388; acute fibrinous pleurisy; acute diphtheritic and hemorrhagic colitis.
9387	16	13 hours.	Very advanced case; incomplete operation; Hg 32%; time of operation 1 hr. 23 min.; surgical shock.
9772	17	12 hours.	Early case; time of operation 2 hrs. 30 min.; patient was pulseless when returned to ward; surgical shock.
9865	19	18 hours.	Moderately early case; time of operation 2 hrs. 35 min.; autopsy No. 1985; showed no direct cause of death; surgical shock.
9920	21	4th day.	Advanced case; time of operation 2 hrs. 10 min.; pulse irregular and thready; cardiac failure.
10016	22	Immediately after wound was closed.	Very advanced case; time of operation 4 hrs. 15 min.; surgical shock.
10084	23	6th day.	Early case; time of operation 2 hrs. 45 min.; severe nausea and vomiting; autopsy No. 2034; cause of death not found; surgical shock.
10296	24	4th day.	Early case; time of operation 1 hr. 45 min.; peritonitis and intestinal obstruction.
10432	26	10th day.	Early case; time of operation 3 hrs.; kidneys showed acute nephritis.
10494	28	4th day.	Very advanced case; time of operation 2 hrs. 35 min.; autopsy; intestinal obstruction.
10505	29	14th day.	Very advanced case; time of operation 3 hrs. 30 min.; abscesses in kidneys (ascending infection).
11367	41	6th day.	Very advanced case; time of operation 3 hrs. 30 min.; autopsy No. 2236; oedema of lungs; fatty degeneration of the liver.
11404	42	17th day.	Advanced case; time of operation 3 hrs. 45 min.; uræmia.
11826	46	14th day.	Advanced case; time of operation 4 hrs.; severe nausea and diarrhoea; asthenia.
11985	47	21st day.	Moderately early case; time of operation 4 hrs. 30 min.; mitral and aortic insufficiency; cardiac collapse on 21st day.
12384	51	7th day.	Early case; time of operation 3 hrs. 40 min.; pneumonia beginning on 2d day.
12610	54	8th day.	Early case; time of operation 2 hrs. 30 min.; autopsy No. 2665; acute, general peritonitis; acute diphtheritic enteritis and colitis; acute splenic tumor; oedema of lungs.
12811	55	13th day.	Very advanced case; time of operation 2 hrs. 25 min.; general peritonitis and intestinal obstruction.
13389	66	11 hours.	Moderately early case; time of operation 3 hrs.; surgical shock.
13555	71	15th day.	Very advanced case; time of operation 2 hrs. 50 min.; autopsy No. 2833; septicaemia.
14236	79	25th day.	Very advanced case; time of operation 3 hrs. 15 min.; apparently cardiac failure.
15548	97	9th day.	Early case; time of operation 2 hrs. 35 min.; general diffuse peritonitis.
16206	109	6th day.	Very advanced case; time of operation 2 hrs. 55 min.; abdomen opened; no peritonitis; surgical shock.
16844	119	10th day.	Very advanced case; time of operation 2 hrs. 10 min.; lobar pneumonia.
17111	122	1/2 hour.	Very advanced case; time of operation 2 hrs. 15 min.; surgical shock.
17607	130	6th day.	Advanced case; time of operation 2 hrs.; general peritonitis.
18020	135	20th day.	Moderately early case; time of operation 3 hrs.; pulmonary embolism.

## SUMMARY OF THE PRIMARY MORTALITY.

Surgical shock .....	9 cases
Peritonitis and intestinal obstruction .....	6 "
Nephritis .....	3 "
Cardiac complications .....	3 "
Pneumonia .....	2 "
Oedema of the lungs .....	1 case
Pleurisy .....	1 "
Pulmonary embolism .....	1 "
Septicæmia .....	1 "
Asthenia .....	1 "
Total .....	28 cases

## PERCENTAGE OF PRIMARY MORTALITY.

Total number of cases.	Total primary deaths.	Total mortality percent.
107	28	26.4
Cases during first 5 years.	Primary deaths during first 5 years.	Mortality percent.
42	14	33.3
Cases during last 5 years.	Primary deaths during last 5 years.	Mortality percent.
65	14	21.5

years it has been 11.5 per cent, a reduction of nearly 50 per cent. Such a decrease in the immediate mortality is very encouraging when the percentage of operability has gradually increased. Obviously, an operator who selects only early cases will have a much lower primary mortality than the one who operates even when there is the slightest hope of saving these patients who are otherwise irretrievably lost. From a study of the primary mortality table, one will notice that the patients dying from the immediate effects of the operation were advanced cases with but few exceptions. The high total primary mortality was due chiefly to two facts, viz., in the earlier years the operation was new, and in many cases included the extensive glandular resection which prolonged the operation greatly, and the patient usually left the table in a tremendously shocked condition. From time to time various procedures have been adopted which have greatly decreased the primary mortality and morbidity.

With increased familiarity of the technique the time required for the completion of the operation has been greatly decreased. Similar operations, formerly requiring from three to five hours, are now completed within practically one-half the time.

*Disinfection of the Growth.*—It has been almost the universal custom to do a preliminary curetage and cauterization of the primary growth. Since nitrous oxide anæsthesia is so generally employed, this may be done several days before the abdominal operation with practically no detriment to the general condition of the patient. This procedure will usually cause a shrinkage of the cervix and increase the mobility, besides allowing time for a more efficient disinfection of the carcinomatous area by antiseptic douches and an improvement in the patient's general condition in this interval by tonics and forced feeding. A most thorough cauterization is done by means of ordinary "soldering irons," which are brought to a glowing heat and introduced deeply into the cervical canal, care being taken not to injure the bladder, rectum and uterine vessels. The cervical canal should also be dilated, since one will occasionally find a pyometra present, which is an absolute indication for the postponement of the operation. For several months the following technique has been employed immediately preceding the abdominal operation and has proved most satisfactory:

(a) The usual perineal and vaginal cleansing—soap and water, bichloride of mercury (1 to 1000) and alcohol, 70 per cent.

(b) Thorough cauterization of the primary growth.

(c) The application of benzine-iodine solution (1 to 1000 iodine) to thoroughly dehydrate the field.

(d) The application of tincture of iodine, 3.5 per cent.

(e) The vaginal canal is packed with iodoform gauze.

Apparently this gives very efficient disinfection, and none of these patients have subsequently developed peritonitis.

*The Incision.*—In all these cases a long, mid-line incision has been employed. In very fat patients, the resection of an ovoid area of skin with the subcutaneous fat in the mid-line (horizontal lipectomy) has been found to be of great advantage. By this method the depth of the field of operation is reduced

about 5 to 7 cm., and the ultimate result adds greatly to the general personal comfort of the patient.

*The Catheterization of the Ureters.*—Although the use of the ureteral catheters has not been followed uniformly, there has been no hesitancy in their employment. With the greater facility of catheterization incident to the improvement of cystoscopic technique, this procedure can be carried out within a few minutes before the general anæsthetic is given and will prove to be of the greatest assistance during the course of the operation. It is especially satisfactory in obese patients, where the exposure is difficult, since it lessens the time necessary for the isolation of the ureters and renders comparatively easy the control of hæmorrhage from the vaginal plexus of veins, which in many cases is the most troublesome part of the entire operation.

From a study of our cases we are led to conclude that the liability of uretero-vaginal fistulæ or secondary infection of the urinary system is not increased by this procedure. However, the following cautions should be observed:

(a) The minimal amount of manipulation with the least possible trauma is to be exercised.

(b) The ureteral sheath should not be disturbed at any point.

(c) The catheters should be removed when the ureters are completely isolated, and further manipulation should consist in rolling the ureters over, with the least possible disturbance to their blood supply.

*The Lymphatic Glands.*—As it is generally conceded that the lymphatic glands are implicated in from one-third to one-half of all operable cases, and since we have no means of determining that involvement except by microscopic examination, theoretically speaking, the ideal operation would include their resection in all cases. However, the present operative facilities and technique do not justify such an extensive operation on account of the great increase in the primary mortality and the probability of incomplete removal if extensive glandular involvement is present. Thus in Wertheim's large series of cases cured, there were only five survivors in whom there was glandular involvement at the time of operation. In our series of cases, for many years no attempt at removal of the lymphatic structures other than those of the parametria has been made.

*The Resection of the Vagina.*—After the thorough dissection of the parametrial and vaginal tissues to a point well below the extent of the growth, they are resected, the vaginal canal being first swabbed out to remove any infected accumulation. With a thorough preliminary cauterization, the widest possible resection with probably the least risk of immediate danger to the patient is obtained by the use of sharp dissection. However, in the more advanced cases the cautery may be employed to incise the vaginal walls and thus possibly destroy small areas of carcinomatous tissue that may remain behind. Here again, great care must be exercised not to injure the bladder, ureters and rectum. In order to get as far beyond the new growth as possible, the vagina, as a whole, is not clamped, but the incised edges are caught, and all hæmorrhage controlled by the application of Ochsner clamps.

As in all abdominal operations, denuded areas should be closed over as completely as is permissible. By this step of the

operation, the liability to post-operative intestinal obstruction is reduced, and the injury to the ureters greatly lessened.

On account of the possible infection present in all cases, some form of pelvic drainage is to be advised. In this clinic, the most satisfactory drainage has been obtained by a small cigarette drain composed of gauze surrounded by rubber protective, placed through the vaginal opening. This drain is loosened on the third or fourth day and removed on the fifth or sixth day. Such a drain serves two important purposes, viz., intestinal obstruction may thus be prevented by taking care of any denuded areas, and also an outlet is provided for any accumulation in the cul de sac.

Occasionally the operative field is widely infected, either by a coincident extensive pelvic inflammation or a separation of the fundus from the cervix. In such cases a small cigarette drain is placed in the lower angle of the incision, which is removed on the second or third day after the operation.

*The Post-operative Treatment.*—Aside from the general measures for combating shock, there are many procedures which may contribute to a smooth convalescence. The excessive trauma to the bladder walls almost invariably causes temporary vesical paralysis, and formerly it was not unusual to catheterize a patient from thirty to forty times. For nearly one and one-half years liquids have been liberally given to all patients until they go to the operating room. This, together with the forcing of liquids practically as soon as the patient becomes conscious and the administration of salt solution by the rectum and by infusion, has reduced the number of catheterizations very markedly. Patients who have been submitted to a definite injury to the bladder are, however, catheterized more frequently to prevent overdistention, and occasionally a retention catheter is left in the bladder for a few days.

As far as possible, the immediate comfort of the patient is to be sought. Probably no one factor contributes more to this end than the employment of the Fowler position.

For several years in the care of these patients the Gatch bed has been employed, by means of which they can occupy the sitting posture. The following advantages are to be gained by such a position:

1. Pelvic drainage is facilitated with a tendency to limit the infection to the pelvic peritoneum.
2. Nausea and vomiting are decreased.
3. Respirations are performed more easily, since the pressure from the distended abdominal viscera upon the diaphragm is greatly lessened.
4. The liability of post-operative pneumonia is greatly decreased by frequent modifications of this posture.

#### POST-OPERATIVE SEQUELÆ.

Uretero-vaginal fistula (bilateral).....	1
Uretero-vaginal fistula (unilateral).....	5
Uretero- and vesico-vaginal fistula.....	1
Vesico-vaginal fistula.....	10
Recto-vaginal fistula.....	4
Cystitis.....	18
Prolapse of bowel.....	1
Incision opened spontaneously.....	2
Phlebitis.....	5



*Post-operative Sequelæ.*—Obviously, the more advanced the carcinomatous growth, the more difficult the operation and the greater are the possibilities of unfortunate post-operative sequelæ. In five cases both ureters were resected and implanted into the bladder; also, in five cases one ureter was treated in like manner; in three cases it was necessary to partially resect the bladder and one ureter; and in one case the bladder alone was partially resected.

As a rule the fistulæ occur late in the convalescence indicating a necrosis through interference of the blood supply. As Sampson has shown, the ureter has a blood supply of its own and can be lifted from its bed near the uterus without necrosis resulting, provided the ureteral sheath is not disturbed. The ureteral sheath is especially resistant to the progress of the carcinomatous growth, so that in advanced cases a certain amount of trauma seems justifiable. Hence a few ureteral fistulæ will occur, which may close spontaneously or will require uretero-vesical implantation later.

In two cases the entire abdominal incision opened about the eighth day. In one case this followed the removal of the stitches, while the other was brought on by a slight attack of coughing. Neither case apparently showed any tendency to heal, and the tissues presented a dull grayish appearance, possibly indicating the presence of a low grade infection. Both patients were taken to the operating room, and the incisions again closed. They both had an uneventful convalescence and are alive and well to-day, one three years and four months and the other, one year and ten months since operation.

In one case (No. 8539) a loop of small bowel prolapsed through the vagina when the pelvic drain was removed. This loop was replaced, a small pack was inserted into the vaginal vault, and the foot of the bed kept elevated until the vaginal opening closed.

By improving the technique and by exercising great care in the manipulations of the ureters, ureteral fistulæ have become very rare. From the table below, one will notice that there has been but one case (No. 120) during the last seven years which subsequently developed uretero-vaginal fistula. This patient was very obese, and exposure of the ureters was quite difficult. During the same period there have been four cases (Nos. 53, 128, 129, 134) which subsequently developed vesico-vaginal fistulæ and three cases (Nos. 110, 111, 131) of recto-vaginal fistulæ.

*Late Results and Absolute Accomplishments.*—Through the efforts of Winter, the statistical study of the end results of carcinoma of the cervix of the uterus has been placed upon a uniform basis, except for the so-called "disappeared" cases. Winter holds that these cases should be deducted, since statistics embracing great numbers of "disappeared" cases have no value whatever, while Wertheim<sup>8</sup> and many other operators contend that such cases should be counted as recurrences.

On undertaking the study of the end results in cases of this clinic, a definite plan for the desired information was adopted and carried out as far as possible. A letter was first sent to the

physician referring the patient to the clinic.\* This plan met with the heartiest coöperation, and many of the patients were personally examined by the physician and an accurate result given. Since the majority of the patients were referred, the amount of clerical work was greatly diminished and more reliable results obtained. Letters were also sent to those patients who were not referred. In case the desired information was not obtained, letters were then sent to relatives and friends. Unfortunately, we have no means of tracing every patient and thus determining the exact result in all cases. Many of our patients come from the colored population whose migratory habits are well known, and after they have changed their residence twice it becomes quite impossible to locate them. However, after a considerable effort, all but ten patients who have been operated upon five years or more have been located and the results thus obtained are here given.

It is quite reasonable to suppose that at least one or more of these "disappeared" cases either had no recurrence or died from an intercurrent disease, which alone would make the percentage of cures untrue and at once depreciate the value of the operation. Hence, if after a diligent and exhaustive search there remain a few patients unlocated, and if these cases are deducted from the total number under consideration, we shall have at least a definite number of patients who have been treated by the extensive abdominal operation and the result of which will be definitely known. However, until this disputed point is settled, all statistical studies should embrace calculations based upon both premises as a basis of comparison of the results obtained in the different clinics.

During the first few years of the period with which this paper deals, the type of operation varied greatly. In all, 13 atypical abdominal operations and 17 vaginal hysterectomies were performed. In many cases an exploratory operation is necessary to determine whether or not a case is operable. From the "Frauenklinik" of Leipzig, out of 221 apparently inoperable cases, reported by Aulhorn,<sup>4</sup> 42 cases or about 20 per cent became apparently operable. Winter,<sup>10</sup> Wertheim,<sup>11</sup> Franz and Zinsser<sup>12</sup> insist that only those cases in which the uterus is not extirpated should be considered exploratory, but if the uterus has been removed, it should be classed as a radical operation. On the other hand, Wertheim<sup>11</sup> classes the patients in which he does a vaginal hysterectomy as inoperable. According to Winter<sup>10</sup> all cases of deaths from operation, without deductions, all cases in which the uterus was extirpated by vaginal, abdominal or combined vaginal and abdominal operations, although cancerous tissue is left behind, and all later deaths where autopsy does not clearly prove that death was due to other causes must be included in the five year period of observation. Statistics based upon cases treated by all operations can be of no value in determining the relative efficiency of any single operation, but merely show what is being accomplished in the treatment of carcinoma cases. To be sure, there must be a dividing line, and the personal factor must be eliminated as far as possible, yet it would seem that the palliative operation

should have a place in combating the terrible symptoms of so dread a malady. In this clinic, all cases are considered palliative in which there has been no attempt at the dissection of the ureters and the removal of the parametria, whether the operation was done to get rid of the mass of the cancerous growth for subsequent treatment with radium or to rid the patient of the almost unbearable symptoms.

In 16 cases (Nos. 7, 15, 21, 35, 50, 51, 52, 55, 69, 93, 100, 110, 119, 123, 124, 136) the operator was conscious of the fact that much cancerous tissue was left behind; yet, since the technique of the extensive operation was employed, these were considered radical and not palliative operations, although the prognosis was apparently hopeless.

Among the 137 cases of extensive abdominal operations, reported above, 82 cases have been operated upon five or more years ago. Of this number, 18 cases have remained well and free from recurrence; 22 cases died as an immediate result of the operation; one case (No. 14) died from intercurrent disease; and ten cases have disappeared.

If we leave out of account the primary mortality and the "disappeared" cases in considering the late results, we have the following:

Eighty-two cases minus 22 operative deaths, 1 death from intercurrent disease, and 10 disappeared = 49. Hence,

$$49:18::100:D$$

$$D=36.7 \text{ per cent cured.}$$

If we include the primary mortality and leave out of account the "disappeared" cases, we have:

$$59:18::100:D'$$

$$D'=30.5 \text{ per cent cured.}$$

If we include both the primary mortality and the "disappeared" cases we have:

$$81:18::100:D''$$

$$D''=22.2 \text{ per cent cured.}$$

From January, 1900, to January, 1908, 99 cases were considered inoperable, seven cases refused operation and the radical operation was done in 82 cases, making a total of 188 cases seeking relief.

From these 188 cases, besides the ten "disappeared" cases and the one case dying from intercurrent disease, seven cases refusing operation must also be deducted according to Werner's<sup>15</sup> method of calculation.

$$188-10-1-\hat{7}=170.$$

Of these 170 cases, 18 remained free from recurrence at least five years, thus giving an "actual accomplishment" of 10.5 per cent.

According to Winter's formula the "actual accomplishments" are as follows:

$$A = \frac{O \times D}{100}.$$

"O" indicates the percentage of operated cases calculated from the number that presented themselves; "D" shows the "late results" (excluding the operative mortality and the "disappeared" cases). Hence,

$$"O" = 188 - 7 \text{ (refused operation) or } 181.$$

$$181:82::100:O.$$

$$O=45.2 \text{ per cent.}$$

$$A = \frac{45.2 \times 36.7}{100}.$$

$$A=16.5 \text{ per cent "actual accomplishment."}$$

*Conclusions.*—From a study of the cases treated at The Johns Hopkins Hospital, the following conclusions are drawn:

1. The extensive abdominal removal of all uterine cervical carcinomata is justified where there is any hope of complete excision, unless there is some special contraindication to surgical interference. This operation, if properly performed, notwithstanding the high primary mortality, has given the greatest percentage of permanent cures of any therapeutic measure thus far suggested.

2. An exploratory operation is often necessary to determine whether or not a case is operable.

3. Obesity is not necessarily a contraindication to the operation, since the wide horizontal lipectomy decreases the depth of the field of operation.

4. The preliminary catheterization of the ureters is a valuable aid, especially in fat patients, and does not necessarily increase the probability of fistulae and secondary infection of the urinary tract.

5. Decreased cervical mobility is sometimes due to a secondary inflammatory reaction and may be improved by a thorough cauterization of the primary growth.

6. Preliminary cauterization and disinfection of the primary growth are advisable in all cases.

7. Extensive glandular dissection is not justified, since the increase in permanent cures does not compensate for the rise in percentage of the primary mortality.

8. By improvements in the technique of the operation, the primary mortality has been decreased from 28.5 per cent for the first seven years to 11.5 per cent for the last five years. Further simplification and perfection of the details of this operation may yet reduce the primary mortality to nearly that of the ordinary laparotomy and make it more generally available.

Aside from the discovery of the etiological factor of carcinoma of the cervix of the uterus and its successful elimination, the greatest hope lies in the early recognition of the primary growth. This can only be accomplished by a more thorough training of the family physician as to the symptoms and signs of cancer and a systematic education of the laity.

TABLE OF CASES OF CARCINOMA OF THE CERVIX OPERATED UPON BY THE MORE RADICAL ABDOMINAL HYSTERECTOMY IN THE GYNECOLOGICAL CLINIC OF THE JOHNS HOPKINS HOSPITAL.

Gynec. No. Date, Serial No.	Age. Prog. Symptoms.	Race.	Path. No. Examination.	Operation.	Immediate result.	Late result.
7729. Jan. 20, 1900. (1)	56 years. White. 1 child; menopause 10 years ago. Bloody vaginal discharge for 1 year; pain over lower spine for 3 months.		Path. No. 3759. Squamous cell carc. cervix.	Prelim. cath. ureters; prelim. curettage; wide abdom. operation, following radical plan of Wertheim and Werder; resection and transplan. of right ureter into bladder. Prognosis, bad.	Disch. Feb. 23, 1900.	Death Oct. 15, 1900, apparently a recurrence.
7827. March 14, 1900. (2)	31 years. Colored. No children. Bloody leucorrhœa for 6 months with slight abd. pain.		Path. No. 3864. Squamous cell carc. cervix.	Prelim. cath. of ureters; wide abdom. operation, following radical plan of Wertheim and Werder. Prognosis, bad.	Disch. April 15, 1900.	Feb., 1912: No recurrence; excellent health.
7814. May 17, 1900. (3)	49 years. White. 2 children. Bloody leucorrhœa for 7 months with bleeding following coitus. Fig. 35.		Path. No. 3974. Squamous cell carc. cervix.	Wide abdom. operation. Glands enlarged. Prognosis, fair.	Ureteral fistula on 14th day. Disch. June 12, 1900.	Dead Sept. 1, 1900; cause unknown.
8348. Oct. 8, 1900. (4)	53 years. White. 11 children; menopause 5 years ago. Bloody discharge for 1 month.		Path. No. missing.	Pelvic cath. ureters; wide abdom. operation. Prognosis, good.	Disch. Nov. 9, 1900.	Feb., 1912: Excellent health; no recurrence.
8304. March 6, 1901. (5)	34 years. White. 3 children. Irregular attacks of bleeding for 4 months.		Path. No. 4745. Squamous cell carc. cervix. Pregnancy 4 months.	Prelim. cath. ureters; wide abdom. operation.	Bowel prolapsed when vag. drain was removed. Disch. March 29, 1901.	Death in 1 year; probably recurrence.
8377. April 4, 1901. (6)	58 years. White. 0 preg. Considerable bleeding daily for 1 month; cramp-like pains under costal angle for 3 months. Fig. 56.		Path. No. 4827. Squamous cell carc. cervix.	Prelim. curettage 3 weeks before; prelim. cath. left ureter; wide abdom. operation. Prognosis, good.	Vesico-vaginal fistula. Disch. April 28, 1901.	Not located.
8480. April 29, 1901. (7)	47 years. White. 4 preg. Irregular menstruation for 2 years with blood tinged leucorrhœa for 2 months.		Path. No. 4901. Squamous cell carc. cervix.	Prelim. curettage with excision of small bit of tissue for diagnosis; prelim. cath. of ureters; wide abdom. operation, incomplete removal. Prognosis, bad.	Death 3d day; surgical shock; PT. never became rational after operation.	
8759. May 25, 1901. (8)	37 years. 8 preg. White. Constant bleeding 3 to 5 months.		Path. No. 4970. Squamous cell carc. cervix.	Pelvic excision for diag.; wide abdom. operation. Prognosis, good.	Disch. June 13, 1901.	Death 3 months after operation, probably a recurrence.
8732. May 16, 1901. (9)	35 years. 7 preg. Bleeding and irritable leucorrhœa for 3 months.		Path. No. 4909. Adenocarc. cervix.	Wide abdom. operation; glands resected, involved. Prognosis, bad.	Disch. June 8, 1901.	Recurrence March, 1902.
8774. May 27, 1901. (10)	45 years. 4 preg. Intermenstrual bleeding for 2 years lasting 10 to 15 days; very offensive, watery discharge for 3 months.		Path. No. 4977. Squamous cell carc. cervix.	Prelim. curettage 5 days before; prelim. cath. ureters; wide abdom. operation. Prognosis, good.	Disch. June 24, 1901.	Feb., 1912: Excellent health; no recurrence.
8887. Aug. 24, 1901. (11)	58 years. White. 9 preg.; menopause 12 years ago. Leucorrhœa, blood tinged 3 months.		Path. No. 5067. Squamous cell carc. cervix.	Excision of portion of cervix for diagnosis; wide abdom. operation. Prognosis, good.	Disch. Sept. 20, 1901.	Death 2 years 11 months from recurrence.
8974. Oct. 10, 1901. (12)	31 years. White. 10 preg. Dull aching pain in pelvis for 6 months.		Path. No. 5222. Squamous cell carc. cervix. 4 months preg.	Prelim. cath. ureters; cauterization of cervix with dilatation and delivery of cervix 2 weeks before; very old, cases bladder involved. Prognosis, bad.	Vesico-vag. fistula. Disch. Nov. 8, 1901.	Death March 14, 1902, recurrence.
8988. Nov. 27, 1901. (13)	60 years. Colored. 7 preg.; menopause 10 years ago. Sharp, shooting pains over lower abd. and thighs for 6 months; severe leucorrhœa 6 months ago and slight constant bleeding since. Fig. 65.		Path. No. 5436. Squamous cell carc. cervix.	Wide abdom. operation. Prognosis, bad.	Disch. Dec. 17, 1901.	Feb., 1909: Excellent health; no recurrence.
9052. Dec. 7, 1901. (14)	64 years. White. 5 preg.; menopause 10 years ago. Irregular bleeding for 2 years. PT. thought menses were returning. Fig. 82.		Path. No. 5447. Squamous cell carc. cervix.	Prelim. vaginal loosening; wide abdom. operation; glands not enlarged. Prognosis, fair.	Vesico-vag. fistula. Disch. Jan. 20, 1902.	Death 1903, from pneumonia.
9062. Feb. 6, 1902. (15)	31 years. White. 6 preg. Thick bloody leucorrhœa for 1½ years.		Path. No. 5573. Squamous cell carc. cervix.	Wide abdom. operation; incomplete resection. Prognosis, bad.	Death 4th day; autopsied 1903; acute fibrinous pleurisy; acute diphtheritic and hemorrhagic colitis.	
9387. Feb. 26, 1902. (16)	46 years. White. 10 preg. Bloody leucorrhœa for 8 months with occasional severe hemorrhage. Fig. 35.		Path. No. 5627. Squamous cell carc. cervix.	Preliminary curettage 20 days before; Prelim. cath. rt. ureter; wide abdom. operation; incomplete. Prognosis, bad.	Death 12 hours later from surgical shock.	
9572. July 16, 1902. (17)	59 years. White. 10 preg.; menopause 9 years ago. Irregular bleeding for 18 months.		Path. No. 5998. Squamous cell carc. cervix.	Prelim. curettage 1 week before; wide abdom. operation.	Death 10 hours later from surgical shock.	
9600. July 26, 1902. (18)	40 years. Colored. 4 preg. Irregular bleeding for 2 years. Fig. 55.		Path. No. 6069. Squamous cell carc. cervix.	Wide abdominal operation; resection of rt. ureter and implantation into bladder. Prognosis, fair.	Vesico-vag. fistula. Disch. Oct. 26, 1902.	Recurrence about 2 months.
9866. Aug. 30, 1902. (19)	54 years. Colored. 6 preg.; menopause 8 years ago. Constant bleeding for 6 months.		Path. No. 6574. Squamous cell carc. cervix.	Prelim. curettage for diag.; prelim. cath. of ureters; wide abdom. operation; resection and implantation of left ureter. Prognosis, bad.	Death following acute thoracic surgical shock.	
9882. Sept. 17, 1902. (20)	44 years. White. 7 preg. Occasional severe bleeding for 6 months with constant watery discharge. Fig. 45.		Path. No. 6169. Squamous cell carc. cervix.	Prelim. cath. ureters; wide abdom. operation; ureters resected and placed into bladder. Prognosis, fair.	Vesico-vag. fistula. Disch. Nov. 11, 1902.	Death 3 months later from pneumonia.
9988. Sept. 25, 1902. (21)	57 years. Colored. 14 preg.; menopause 15 years ago. Irregular bleeding for 2 months. Fig. 75.		Path. No. 6717. Squamous cell carc. cervix.	Prelim. cath. ureters; wide abdom. operation; incomplete.	Death following acute thoracic surgical shock.	
10116. Oct. 25, 1902. (22)	40 years. White. 6 preg. Increased menstrual flow for several months; offensive, irritating discharge for 3 months.		Path. No. 6197. Squamous cell carc. cervix.	Prelim. curettage; wide abdom. operation; resection of both ureters and implantation into bladder.	Death from surgical shock shortly after incision was closed.	



TABLE OF CASES OF CARCINOMA OF THE CERVIX OPERATED UPON BY THE MORE RADICAL ABDOMINAL HYSTERECTOMY IN THE GYNECOLOGICAL CLINIC OF THE JOHNS HOPKINS HOSPITAL—Continued.

Case No. Date.	Age. Preg. Race. Symptoms.	Path. No. Examination.	Operation.	Immediate result.	Later result.
10084 Nov. 20, 1902. (29)	44 years. White. Leucorrhœa for 3 months.	Path. No. 6284. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, fair.	Death 6th day; autopsy, 2034; cause of death not found.	
10296 March 14, 1903. (24)	44 years. White. 6 preg. Inter-menstrual bleeding for 3 months; pain over lower abd. Hg. 60.	Path. No. 6315. Squamous cell carcinoma.	Prelim. curettage 2 weeks before; preim. cath. rt. ureter; wide abdom. operation. Prognosis, fair.	Death 4th day from intestinal obstruction and peritonitis.	
10094 March 18, 1903. (25)	54 years. White. 8 preg. Profuse irritating leucorrhœa for 2 years. Hg. 70.	Path. No. 6347. Squamous cell carcinoma.	Prelim. cath. ureters; wide abdom. operation. Prognosis, fair.	Vesico-vaginal fistula. Disch. June 6, 1903.	March, 1911: Enjoying the best of health.
10442 April 29, 1903. (26)	62 years. White. 2 preg.; menopause 9 years ago. Dull pain over abdomen for 2 years; first bleeding 7 weeks ago while at stool. Hg. 68.	Path. No. 6660. Squamous cell carcinoma.	Prelim. cath. ureters; wide abdom. operation. Prognosis, good.	Death 14th day, uræmia, acute nephritis.	
10444 May 6, 1903. (27)	56 years. White. 6 preg.; menopause 12 years ago. Irreg. bleeding for 7 months. Hg. 74.	Path. No. 6686. Squamous cell carcinoma.	Prelim. cath. ureters; wide abdom. operation.	Cystitis. Disch. June 22, 1903.	April, 1913: Entirely well since operation.
10494 May 16, 1903. (28)	36 years. White. 7 preg. Inter-menstrual bleeding for 4 months.	Path. No. 6777. Squamous cell carcinoma.	Wide abdom. operation: resection of bladder and rt. ureter, very advanced case.	Death 4th day; autopsy: intestinal obstruction.	
10505 May 27, 1903. (29)	43 years. White. 6 preg. Menorrhagia for 2 months. Hg. 70.	Path. No. 6747. Squamous cell carcinoma.	Wide abdom. operation: resection and implantation of both ureters; very advanced case.	Death 11th day, acute pyelonephritis.	
10523 June 3, 1903. (30)	41 years. White. 1 preg. Mal-odorous, profuse leucorrhœa for 2 years; considerable bleeding for 3 weeks.	Path. No. 6745. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, fair.	Cystitis with probable uretero-vag. fistula. Disch. July 3, 1903.	Not located.
10603 July 18, 1903. (31)	58 years. White. 13 preg.; menopause 1½ years ago. Slight blood-tinged leucorrhœa since.	Path. No. 6887. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, good.	Cystitis. Disch. Aug. 27, 1903.	March, 1912: Enjoying excellent health.
10609 July 20, 1903. (32)	48 years. White. 5 preg. Occasional attacks of bleeding for 18 months; pain over abd. and thighs for 4 months; frequent urination for 1 month. Hg. 80.	Path. No. 6866. Squamous cell carcinoma.	Prelim. cath. ureters; wide abdom. operation. Prognosis, fair.	Uretero-vag. fistula (left). Disch. Aug. 27, 1903.	Death April, 1905, from recurrence.
10657 Oct. 3, 1903. (33)	39 years. White. 4 preg. Dragging sensation in pelvis for 5 months; no bleeding.	Path. No. 6887. Squamous cell carcinoma.	Prelim. cath. ureters; wide abdom. operation; bladder injured. Prognosis, bad.	Vesico-vag. fistula. Disch. Oct. 20, 1903.	Feb., 1911: Entirely well.
10648 Nov. 12, 1903. (34)	55 years. White. 1 preg. Pain over lower abdomen.	Path. No. 7077. Squamous cell carcinoma.	Prelim. cath. ureters; wide abdom. operation. Prognosis, fair.	Disch. Dec. 16, 1903.	Recurrence April, 1904.
11184 March 31, 1904. (35)	33 years. Colored. 2 preg. Bleeding after douching and coitus for 6 months. Hg. 75.	Path. No. 7370. Squamous cell carcinoma.	Prelim. cath. left ureter; wide abdom. operation; incomplete removal.	Cystitis. Disch. May 24, 1904.	Not located.
11192 May 16, 1904. (36)	37 years. White. 6 preg. Blood-tinged leucorrhœa for 10 months; pain over lower abd. 8 months. Hg. 73.	Path. No. 7414. Squamous cell carcinoma.	Wide abdom. operation: rectum, involved; advanced case.	Recto-vag. fistula, sh. disch. Disch. Nov. 24, 1904.	Death 3 months later from recurrence.
11225 May 2, 1904. (37)	50 years. White. 2 preg. Bleeding after stool for 3 months. Hg. 74.	Path. No. 7405. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, good.	Disch. May 30, 1904.	Oct., 1911: In excellent health.
11234 May 5, 1904. (38)	47 years. White. 7 preg. Menorrhagia for 2 years; constant bleeding for 3 months. Hg. 55.	Path. No. 7498. Squamous cell carcinoma.	Prelim. cath. ureters; wide abdom. operation; ureters resected and implanted; bladder involved.	Cystitis; uretero and vesico-vag. fistula. Disch. Aug. 24, 1904.	Not located.
11292 June 5, 1904. (39)	57 years. White. 4 preg. Irregular menses, 8 months; bleeding while at stool.	Path. No. 7601. Squamous cell carcinoma.	Prelim. cath. ureters; wide abdom. operation. Prognosis, good.	Cystitis. Disch. June 24, 1904.	Feb., 1912: In excellent health.
11296 June 23, 1904. (40)	40 years. White. 3 preg. "Soreness" in womb for 1 year; bloody disch. for 7 months. Hg. 70.	Path. No. 7602. Squamous cell carcinoma.	Wide abdom. operation.	Cystitis; uretero-vag. fistula, 18th day. Spontaneous closure. Disch. July 27, 1904.	April, 1912: In excellent health.
11267 June 27, 1904. (41)	63 years. Colored. 7 preg.; menopause 17 years ago. Vag. bleeding 5 years ago; occasional attacks since. Hg. 85.	Path. No. 7658. Squamous cell carcinoma.	Wide abdom. operation: resection of both ureters.	Death 6th day; autopsy, 2336; edema of lungs.	
11404 July 20, 1904. (42)	38 years. White. 7 preg. Hysterectomy, 4 years ago; occasional bleeding for 8 months.	Path. No. 7800. Squamous cell carcinoma.	Wide abdom. operation: resection of bladder.	Death 17th day, uræmia.	
11571 Jan. 4, 1905. (43)	60 years. White. 9 preg.; menopause 10 years ago. Prof. leucorrhœa for 3 years.	Path. No. 8152. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, good.	Disch. Feb. 2, 1905.	Not located.
11784 Jan. 7, 1905. (44)	29 years. Colored. 1 preg. Watery disch. for 2½ months; bleeding on examination. Hg. 65.	Path. No. 8200. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, good.	Phlebitis, 11th day. Disch. Feb. 19, 1905.	Not located.
11846 Jan. 19, 1905. (45)	30 years. Colored. 1 preg. Inter-menstrual bleeding 4 months with watery disch.	Path. No. 8155. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, good.	Cystitis. Disch. April 1, 1905.	Not located.
11826 Jan. 25, 1905. (46)	62 years. White. 4 preg.; menopause 17 years ago. Bloody leucorrhœa 7 months.	Path. No. 8204. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, bad.	Death 14th day; as-thenia.	
11845 March 28, 1905. (47)	44 years. White. 8 preg. Slight inter-menstrual bleeding for 5 years; constant for 9 months.	Path. No. 8416. Squamous cell carcinoma.	Prelim. curettage; wide abdom. operation.	Death 21st day, cardiac failure (mitral and aortic insufficiency).	

TABLE OF CASES OF CARCINOMA OF THE CERVIX OPERATED UPON BY THE MORE RADICAL ABDOMINAL HYSTERECTOMY IN THE GYNECOLOGICAL CLINIC OF THE JOHNS HOPKINS HOSPITAL—Continued.

Gynec. No. Date, Serial No.	Age. Race. Preg. Symptoms.	Path. No. Examination.	Operation.	Immediate result.	Later result.
12969. April 20, 1905. (48)	36 years. White. 4 preg.; menopause 2 years ago. Brown-colored leucorrhœa for 3 months.	Path. No. 8602. Squamous cell carc. cervix; adeno-myoma of the uterus.	Wide abdom. operation. Prognosis, good.	Disch. Mar. 21, 1905.	Not located.
12984. June 17, 1905. (49)	28 years. White. 1 preg. Blood-tinged leucorrhœa with pain for 5 months.	Path. No. 8771. Squamous cell carc. cervix.	Wide abdom. operation. Prognosis, good.	Thrombosis of left femoral vein 12th day. Disch. July 31, 1905.	Death Dec. 3, 1905; cause, doubtful.
12244. July 19, 1905. (50)	50 years. Colored. 2 preg.; menopause 16 years ago. Bloody vag. disch. for 8 months; polyuria.	Path. No. 8840. Adeno-car. cervix and body of uterus.	Wide abdom. operation; incomplete; very advanced case.	Disch. Aug. 11, 1905.	Death March 2, 1906; from recurrence.
12294. Aug. 18, 1905. (51)	50 years. White. 7 preg.; menopause 1 year ago. Slight bleeding for last 7 months with watery disch.	Path. No. 8896. Squamous cell carc. cervix.	Wide abdom. operation; incomplete; very advanced case.	Death 7th day from pneumonia.	
12241. Oct. 21, 1905. (52)	49 years. Colored. 11 preg. Irregular bleeding for 8 months.	Path. No. 9067. Squamous cell carc. cervix.	Wide abdom. operation; incomplete; very advanced case.	Disch. Nov. 9, 1905.	Death March 25, 1907; from recurrence.
12297. Jan. 19, 1906. (53)	37 years. White. 3 preg. Watery disch. for 6 months with much bleeding for 3 months.	Path. No. 9369. Squamous cell carc. cervix with metastases to vagina.	Pelvic curettage; wide abdom. operation. Prognosis, fair.	Vesico-vag. fistula 12th day; closed by operation. Disch. March 6, 1906.	Feb., 1912: In excellent health; no recurrence.
12910. Jan. 22, 1906. (54)	32 years. Colored. 3 preg. Sudden hemorrhages for 3 months.	Path. No. 9372. Squamous cell carc. cervix; myoma uteri.	Prelim. curettage 1 week before; prelim. cath. ureters; wide abdom. operation.	Death 18th day; autopsy: general peritonitis; edema of lungs.	
12931. Jan. 4, 1906. (55)	56 years. Colored. 6 preg.; menopause 6 years ago. Severe bleeding every month for 5 months. Fig. 55.	Path. No. 9395. Squamous cell carc. cervix.	Pelvic curettage; wide abdom. operation; incomplete; very advanced case.	Death 13th day; autopsy: general peritonitis.	
12540. Jan. 29, 1906. (56)	40 years. White. 2 preg. Slight intermenstrual bleeding for 6 months.	Path. No. 9389. Squamous cell carc. cervix; myoma uteri.	Pelvic curettage 1 week before; wide abdom. operation. Prognosis, good.	Cystitis. Disch. March 6, 1906.	Death Jan. 21, 1907; from recurrence.
12914. May 15, 1906. (57)	37 years. White. 6 preg.; youngest child 1 month old. Irritating leucorrhœa for 4 months.	Path. No. 9812. Squamous cell carc. cervix.	Curettage 6 days before; wide abdom. operation. Prognosis, good.	Disch. June 8, 1906.	March, 1912: No recurrence.
12948. May 14, 1906. (58)	42 years. Colored. 4 preg. Irregular bleeding for 6 months; profuse for 1 month. Fig. 59.	Path. No. 9841. Squamous cell carc. cervix.	Wide abdom. operation. Prognosis, fair.	Disch. June 2, 1906.	Not located.
12969. May 28, 1906. (59)	22 years. White. 1 preg. Blood-tinged leucorrhœa for 6 months.	Path. No. 9876. Adeno-car. cervix; metastases to lymph glands; indurations on vaginal wall.	Wide abdom. operation. Prognosis, bad.	Disch. June 28, 1906.	Not located.
12987. June 7, 1906. (60)	50 years. White. 6 preg. Slight bleeding for 6 months.	Path. No. 10242. Squamous cell carc. cervix.	Wide abdom. operation. Prognosis, good.	Disch. June 27, 1906.	Feb., 1912: Excellent health.
12950. July 5, 1906. (61)	56 years. White. 3 preg.; menopause 10 years ago. Bleeding for 4 months.	Path. No. 10235. Squamous cell carc. cervix.	Wide abdom. operation. Prognosis, good.	Disch. Aug. 3, 1906.	Death Sept. 4, 1907; from recurrence.
12956. July 5, 1906. (62)	42 years. White. 0 preg. Irregular bleeding for 3 months; constant watery disch. for 2 months.	Path. No. 10067. Squamous cell carc. cervix; myomata uteri; pelvic inflammation.	Wide abdom. operation. Prognosis, good.	Disch. Aug. 20, 1906.	Death.
12940. Sept. 10, 1906. (63)	54 years. White. 2 preg.; menopause 8 years ago. Scanty blood-tinged disch. for several weeks.	Path. No. 10430. Squamous cell carc. cervix.	Pelvic excision for diagnosis; wide abdom. operation.	Cystitis. Disch. Oct. 11, 1906.	Death June 19, 1908, hemorrhages from bowel (recurrence).
12909. Oct. 30, 1906. (64)	37 years. White. 2 preg. Irregular bleeding for 5 months.	Path. No. 10456. Squamous cell carc. cervix.	Pelvic curettage; wide abdom. operation. Prognosis, bad.	Cystitis. Disch. Nov. 12, 1906.	Death about 2 years later from recurrence.
12917. Oct. 21, 1906. (65)	25 years. White. 0 preg. Blood-tinged leucorrhœa for 1 year.	Path. No. 10446. Squamous cell carc. cervix; metastases to glands.	Prelim. curettage 1 month before; wide abdom. operation. Prognosis, bad.	Cystitis. Disch. Dec. 22, 1906.	Death 6 months later; from recurrence.
12909. Nov. 17, 1906. (66)	47 years. White. 0 preg. Irritating disch. for 6 to 8 weeks.	Path. No. 10582. Squamous cell carc. cervix.	Pelvic curettage; wide abdom. operation. Prognosis, advanced case.	Disch. 11 days later; from advanced case.	
12945. Nov. 17, 1906. (67)	52 years. White. 7 preg.; menopause 3 years ago. Brownish vag. disch. for 4 months; "bearing down" pains over lower abdom. for 6 weeks.	Path. No. 10702. Squamous cell carc. cervix; myoma uteri.	Pelvic curettage; wide abdom. operation. Prognosis, fair.	Disch. Nov. 1, 1907.	Feb., 1912: No recurrence.
12943. Dec. 26, 1906. (68)	50 years. White. 8 preg.; menopause 35 years ago. Occasional blood stain on clothing for 4 months.	Path. No. 10698. Squamous cell carc. cervix.	Pelvic excision for diagnosis; wide abdom. operation. Prognosis, good.	Cystitis. Disch. Jan. 24, 1907.	Death Dec. 1, 1907; from recurrence.
12925. Jan. 26, 1907. (69)	54 years. White. 6 preg.; menopause 4 years ago. Irregular bleeding for 6 months.	Path. No. 10702. Squamous cell carc. cervix.	Wide abdom. operation; incomplete.	Disch. March 4, 1907.	Inoperable mass in pelvis, July 15, 1907.
12945. Feb. 1, 1907. (70)	52 years. Colored. 3 preg.; menopause 1 year ago. Irregular bleeding for 8 months. Fig. 60.	Path. No. 10845. Squamous cell carc. cervix.	Wide abdom. operation; very advanced case.	Disch. April 3, 1907.	Death.

TABLE OF CASES OF CARCINOMA OF THE CERVIX OPERATED UPON BY THE MORE RADICAL ABDOMINAL HYSTERECTOMY IN THE GYNECOLOGICAL CLINIC OF THE JOHNS HOPKINS HOSPITAL—Continued.

Case No. Date, Serial No.	Age. Preg. Race. Symptoms	Path. No. Examination.	Operation.	Immediate result.	Late result.
14137. Feb. 12, 1907. (71)	47 years. White. 1 preg.; menopause 36 years ago. Irregular bleeding for 4 months.	Path. No. 11840. Squamous cell carcinoma.	Wide abdom. operation; resection of bladder wall and rt. ureter; very advanced case.	Death 15th day, septicæmia; autopsy.	
14229. May 17, 1906. (72)	47 years. White. 2 preg.; menopause 3 years ago. Irregular bleeding since.	Path. No. 11841. Squamous cell carcinoma.	Wide abdom. operation.	Disch. June 4, 1906.	Death July 6, 1907, from recurrence.
14236. July 8, 1907. (73)	56 years. White. 5 preg.; menopause 7 years ago. Irregular bleeding for 1 year.	Path. No. 11842. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, fair.	Disch. Aug. 14, 1907.	Death May, 1908, from recurrence.
14662. Aug. 6, 1907. (74)	55 years. White. 6 preg.; menopause 18 years ago. Irregular bleeding for 4 months.	Path. No. 11854. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, good.	Disch. Sept. 1, 1907.	March, 1912: No recurrence.
14126. Aug. 27, 1907. (75)	59 years. Colored. 6 preg. Irregular bleeding for 8 months.	Path. No. 11826. Squamous cell carcinoma; necrosis uteri.	Wide abdom. operation. Prognosis, good.	Disch. Oct. 3, 1907.	Not located.
14127. Aug. 26, 1907. (76)	45 years. White. 5 preg. Blood-tinged leucorrhœa for 7 months; pains in hips.	Path. No. 11848. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, good.	Disch. Sept. 23, 1907.	Death May 12, 1909; probable recurrence.
14129. Aug. 29, 1907. (77)	41 years. White. Irregular bleeding for 2 months.	Path. No. missing.	Prelim. curettage; wide abdom. operation. cath. left ureter; wide abdom. operation.	Phlebitis 11th day (left). Disch. Oct. 6, 1907.	March, 1913: Patient writes, she is in good health, perfectly cured.
14141. Sept. 2, 1907. (78)	58 years. White. 6 preg.; menopause 13 years ago. Irregular bleeding for last 3 years.	Path. No. 11845. Adenocarc. cervix.	Prelim. curettage; wide abdom. operation.	Disch. Sept. 28, 1907.	Death Feb., 1910, from recurrence.
14236. Oct. 4, 1907. (79)	44 years. White. 1 preg. Constant bleeding for last 9 months.	Path. No. 11848. Squamous cell carcinoma.	Wide abdom. operation with resection of ureter and bladder; very advanced case.	Death 25th day; cause not given; apparently cardiac complications.	
14225. Nov. 1, 1907. (80)	55 years. White. 0 preg.; menopause 5 years ago. Irregular bleeding for 7 months.	Path. No. 11867. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, good.	Disch. Nov. 24, 1907.	March, 1913: In excellent health.
14188. Nov. 27, 1907. (81)	21 years. White. 0 preg. Leucorrhœa for 6 months; pain over lower abdom. for 3 months.	Path. No. 11880. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, bad.	Disch. Dec. 20, 1907.	Death 18 months after operation, recurrence.
14187. Dec. 2, 1907. (82)	57 years. White. 8 preg.; menopause 2 years ago. Irritating blood-tinged leucorrhœa for 1½ years.	Path. No. 12145. Squamous cell carcinoma.	Prelim. curettage; wide abdom. operation.	Disch. Dec. 24, 1907.	Death Dec. 8, 1908, from recurrence.
14469. Jan. 6, 1908. (83)	59 years. White. 6 preg. Irregular menses for 3 years; bleeding after coitus for 1 year.	Path. No. 12242. Squamous cell carcinoma.	Prelim. cauterization 4 days before; prelim. cath. left ureter; wide abdom. operation; very advanced case.	Phlebitis, left; 14th day. Disch. March 20, 1908.	Death July 10, 1908, probable recurrence.
14485. Jan. 11, 1908. (84)	36 years. White. 1 preg. Bleeding following coitus for 4 months.	Path. No. 12182. Squamous cell carcinoma; metastases to lymph glands.	Wide abdom. operation. Prognosis, bad.	Disch. Feb. 3, 1908.	Not located.
14552. Feb. 3, 1908. (85)	52 years. White. 7 preg. Irregular menses for 1 year.	Path. No. 12254. Squamous cell carcinoma.	Prelim. curettage and cauterization; wide abdom. operation. Prognosis, good.	Disch. March 12, 1908.	Death Nov. 19, 1909, from recurrence.
14553. Feb. 8, 1908. (86)	27 years. White. 2 preg. Irregular bleeding for 18 months.	Path. No. 12251. Squamous cell carcinoma.	Wide abdom. operation.	Disch. March 5, 1908.	Not located.
14557. Feb. 10, 1908. (87)	56 years. White. 7 preg.; menopause 11 years ago. Irregular bleeding and watery disch. for 6 months.	Path. No. 12252. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, good.	Phlebitis, left. Disch. March 14, 1908.	March 22, 1913: In excellent health.
14561. Feb. 15, 1908. (88)	45 years. White. Irregular bleeding for 6 months; polyuria and painful defecation for 2 months.	Path. No. 12253. Squamous cell carcinoma.	Prelim. curettage and cauterization; wide abdom. operation; rectum adherent.	Cystitis. Disch. March 24, 1908.	Death June 4, 1909, probable recurrence.
14597. Feb. 29, 1908. (89)	47 years. White. 5 preg. Constant bleeding for 1 month.	Path. No. 12237. Adeno-carc. cervix; bilateral ovarian carcinoma.	Wide abdom. operation. Prognosis, fair.	Disch. April 13, 1908.	Not located.
14692. April 14, 1908. (90)	42 years. White. 1 preg. Constant bloody disch. for 4 months; profuse bleeding after straining at stool.	Path. No. 12456. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, good.	Disch. April 24, 1908.	Death 3 months later from recurrence.
14894. May 29, 1908. (91)	45 years. Colored. 5 preg. Severe leucorrhœa for 2 months; blood-tinged for 3 weeks.	Path. No. 12636. Squamous cell carcinoma.	Prelim. curettage and cauterization; wide abdom. operation, incomplete removal.	Disch. July 2, 1908.	Death.
14911. June 27, 1908. (92)	45 years. White. 4 preg. Irregular menses with very profuse bleeding for the last 2 months; polyuria.	Path. No. 12637. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, good.	Cystitis. Disch. July 16, 1908.	March 27, 1913: Excellent health; no recurrence.
14946. July 6, 1908. (93)	45 years. White. 8 preg.; menopause 8 years ago. Irregular bleeding for 1 year.	Path. No. 12812. Squamous cell carcinoma; cervix with pyometra.	Prelim. cauterization; wide abdom. operation; incomplete removal. Prognosis, hopeless.	Disch. Aug. 8, 1908.	Death May 29, 1911; recurrence.
15053. Aug. 23, 1908. (94)	49 years. Colored. 3 preg. Blood-tinged leucorrhœa for 3 months with pain over lower abdom.	Path. No. 12923. Squamous cell carcinoma.	Prelim. cauterization; wide abdom. operation. Prognosis, good.	Disch. Sept. 12, 1908.	March, 1913: In good health.
15080. Nov. 27, 1908. (95)	55 years. White. 3 preg.; menopause 10 years ago. Blood-tinged leucorrhœa for 2 years.	Path. No. 12927. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, good.	Disch. Dec. 27, 1908.	Death Oct., 1909; probable recurrence.



TABLE OF CASES OF CARCINOMA OF THE CERVIX OPERATED UPON BY THE MORE RADICAL ABDOMINAL HYSTERECTOMY IN THE GYNECOLOGICAL CLINIC OF THE JOHNS HOPKINS HOSPITAL—Continued.

Gynec. No. Date. Serial No.	Age. Race. Preg. Symptoms.	Path. No. Examination.	Operation.	Immediate result.	Late result.
15496. Jan. 13, 1909. (90)	65 years. White. 3 preg.; menopause 10 years ago. Irritating leucorrhoea for 2½ years.	Path. No. 13370. Squamous cell carc. cervix.	Wide abdom. operation. Prognosis, good.	Disch. Feb. 2, 1909.	April, 1910. No evidence of recurrence.
15548. March 10, 1909. (97)	58 years. Colored. 9 preg.; menopause 18 years ago. Blood-tinged leucorrhoea for 1 year; pain over lower abdom. for 6 months.	Path. No. 13379. Squamous cell carc. cervix.	Prelim. curettage for diagnosis; wide abdom. operation; very advanced case.	Death 9th day; anæsthesia, general peritonitis.	
15782. May 24, 1909. (98)	55 years. White. 9 preg.; menopause 10 years ago. Blood-tinged leucorrhoea for 6 weeks.	Path. No. 13849. Squamous cell carc. cervix; myoma of uterus.	Wide abdom. operation; resection of left ureter; very advanced case.	Disch. June 27, 1909.	Not located.
15767. June 5, 1909. (99)	47 years. White. 0 preg. Blood-tinged disch. for 1 month.	Path. No. 12968. Squamous cell carc. cervix.	Wide abdom. operation; advanced case.	Disch. June 27, 1909.	Death.
15872. July 5, 1909. (100)	50 years. Colored. 5 preg.; menopause 5 years ago. Irregular bleeding for 18 months.	Path. No. 14002. Squamous cell carc. cervix.	Prelim. curettage; wide abdom. operation; incomplete removal; very advanced case.	Disch. Aug. 2, 1909.	Feb. 22, 1912: Advanced recurrence.
15889. Aug. 7, 1909. (101)	61 years. White. 1 preg.; menopause 14 years ago. Irregular bleeding for 1 year.	Path. No. 14082. Squamous cell carc. cervix.	Wide abdom. operation.	Disch. Oct. 6, 1909.	Not located.
15978. Aug. 24, 1909. (102)	55 years. White. 3 preg.; menopause 9 years ago. Blood-tinged leucorrhoea for 11 months.	Path. No. 14129. Squamous cell carc. cervix.	Prelim. cauterization; wide abdom. operation. Prognosis, good.	Disch. Sept. 18, 1909.	Death Nov. 17, 1910; recurrence.
15977. Aug. 23, 1909. (103)	54 years. White. 1 preg. Profuse menorrhagia with almost constant sanguineous disch. for 3 years.	Path. No. 14117. Squamous cell carc. cervix.	Prelim. cauterization; wide abdom. operation. Prognosis, good.	Disch. Oct. 16, 1909.	April, 1912, in excellent health.
16104. Oct. 27, 1909. (104)	31 years. White. 2 preg. Irregular bleeding for 4 months.	Path. No. 14365. Squamous cell carc. cervix.	Prelim. cauterization 1 week before; wide abdom. operation; very advanced case.	Disch. Nov. 13, 1909.	Not located.
16112. Oct. 28, 1909. (105)	35 years. Colored. 4 preg. Pain over lower abdom. for 3 months.	Path. No. 14397. Squamous cell carc. cervix; pelvic inflam. disease.	Excision of pelvic abscess with removal of part of cervix for diagnosis. Prelim. cath. ureters. Prognosis, good.	Disch. Nov. 14, 1909.	March, 1912: No evidence of recurrence when last seen. Has left the city.
16133. Oct. 26, 1909. (106)	48 years. White. 3 preg. Intermenstrual bleeding for 3 months.	Path. No. 14335. Squamous cell carc. cervix.	Prelim. cath. ureters; prelim. cauterization; wide abdom. operation; advanced case.	Disch. Nov. 24, 1909.	Recurrence Sept., 1910.
16132. Nov. 15, 1909. (107)	51 years. White. 8 preg.; menopause 5 years ago. Irregular bleeding for 5 months. Hg. 43.	Path. No. 14418. Squamous cell carc. cervix.	Prelim. cauterization for inoperable case. Such marked improvement in 2 weeks, growth was removed; advanced case.	Disch. Dec. 7, 1909.	March, 1913: In excellent health; no recurrence.
16176. Nov. 6, 1909. (108)	49 years. Colored. 4 preg.; menopause 4 years ago. Irregular bleeding after straining at stool for 5 months; pain over lower abdom. for 7 months.	Path. No. 14375. Squamous cell carc. cervix; myoma uteri.	Wide abdom. operation; advanced case.	Incision opened on 8th day. Disch. Jan. 4, 1910.	March, 1913: In excellent health.
16206. Dec. 1, 1909. (109)	44 years. White. 3 preg. Irregular bleeding and constant blood-tinged disch. which was irritating for 6 months. Painful urination and defecation.	Path. No. 14743. Squamous cell carc. cervix.	Prelim. cauterization 4 days before; wide abdom. operation; very advanced case.	Death 6th day; probably surgical shock; no peritonitis.	
16298. Jan. 5, 1910. (110)	26 years. Colored. 4 preg. Severe pain over lower abdom. for 2 months.	Path. No. 14567. Squamous cell carc. cervix.	Wide abdom. operation; incomplete removal; very advanced case.	Recto-vag. fistula. Disch. March 5, 1910.	Not located.
16344. Jan. 26, 1910. (111)	29 years. Colored. 0 preg. Constant bleeding for 2 months.	Path. No. 14911. Squamous cell carc. cervix.	Wide abdom. operation; advanced case.	Recto-vag. fistula. Disch. March 17, 1910.	Not located.
16374. Jan. 27, 1910. (112)	35 years. Colored. 7 preg.; menopause 6 years ago. Severe pain over lower spine with blood-tinged leucorrhoea for 4 months.	Path. No. 14643. Squamous cell carc. cervix.	Prelim. cauterization; wide abdom. operation.	Cystitis. Disch. Feb. 15, 1910.	Death Nov. 1911, from recurrence.
16256. Feb. 14, 1910. (113)	35 years. White. 7 preg.; menopause 3 years ago. Irregular bleeding for 6 months.	Path. No. 14791. Squamous cell carc. cervix.	Prelim. cauterization; wide abdom. operation; removal of gall stones. Prognosis, good.	Disch. March 24, 1910.	Recurrence Sept., 1913.
16462. March 10, 1910. (114)	37 years. White. 5 preg. Pain over lower abdom. for 4 months.	Path. No. 14822. Squamous cell carc. cervix.	Prelim. cauterization; wide abdom. operation. Prognosis, good.	Disch. April 4, 1910.	Not located.
16661. May 18, 1910. (115)	47 years. White. 5 preg. Irregular bleeding for 6 months.	Path. No. 15002. Adenocarc. cervix.	Prelim. cauterization; wide abdom. operation. Prognosis, good.	Death, July 8, 1910.	Jan., 1912: In good health; no recurrence.
16692. June 2, 1910. (116)	29 years. White. 1 preg. Irregular bleeding for 5 months. Hg. 65.	Path. No. 15110. Squamous cell carc. cervix.	Prelim. excision for diag; wide abdom. operation.	Cystitis. Disch. June 23, 1910.	Death March 8, 1911, from tuberculosis.
16757. June 22, 1910. (117)	65 years. White. 6 preg.; menopause 15 years ago. Blood-tinged leucorrhoea for 2 months.	Path. No. 15299. Adenocarc. cervix.	Prelim. cauterization; wide abdom. operation. Prognosis, good.	Disch. July 12, 1910.	Death July 1911, from tuberculosis.
16868. July 23, 1910. (118)	57 years. White. 4 preg.; menopause 10 years ago. Irregular bleeding with irritating leucorrhoea for 10 months.	Path. No. 15256. Squamous cell carc. cervix.	Prelim. cauterization 1 week before; wide abdom. operation. Prognosis, good.	Disch. Sept. 10, 1910.	Recurrence June 1911, from metastasis.
16944. Aug. 4, 1910. (119)	52 years. White. 6 preg.; menopause 1 year ago. Constant bleeding for 4 months.	Path. No. 15202. Squamous cell carc. cervix.	Prelim. curettage and cauterization 1 week before; wide abdom. operation; incomplete removal.	Death 15th day; lobar pneumonia.	

TABLE OF CASES OF CARCINOMA OF THE CERVIX OPERATED UPON BY THE MORE RADICAL ABDOMINAL HYSTERECTOMY IN THE GYNECOLOGICAL CLINIC OF THE JOHNS HOPKINS HOSPITAL—Continued.

Clinical No. Date Serial No.	Age. Race. Symptoms	Path. No. Examination	Operation.	Immediate result.	Late result.
17027 Oct. 31, 1910. (120)	44 years. Colored. 6 preg. Watery discharge for 2 months; dull, aching pain over lower abdomen, for 2 months.	Path. No. 13632. Squamous cell carcinoma.	Wide abdom. operation. Prognosis, good.	Utero-vaginal fistula on 6th day. Disch. Nov. 18, 1910.	Not located.
17088 Nov. 19, 1911. (121)	47 years. White. 2 preg. Irregular bleeding with profuse watery disch. for 3 years.	Path. No. 13660. Adenocarc. cervix.	Cauterization 2 weeks before; prelim. cath. of rt. ureter; wide abdom. operation. Prognosis, fair.	Disch. Dec. 10, 1910.	March, 1913: In good health.
17111. Nov. 19, 1910. (122)	47 years. White. 7 preg. Irregular bleeding for 2 years; dysuria 1 1/2 years.	Path. No. 13445. Adenocarc. cervix.	Cauterization 4 days before; wide abdom. operation.	Death 1 1/2 hour later from surgical shock.	
17124 Nov. 26, 1910. (123)	42 years. Colored. 5 preg. Irregular bleeding for 5 months. Hg. 65.	Path. No. 13754. Squamous cell carcinoma.	Cauterization 1 week before; wide abdom. operation; incomplete removal.	Disch. Dec. 15, 1910.	Death.
17136 Jan. 6, 1910. (124)	47 years. Colored. 2 preg. Irregular bleeding for 5 months.	Path. No. 13770. Squamous cell carcinoma.	Preliminary cauterization; wide abdom. operation; incomplete removal.	Disch. Dec. 20, 1910.	Not located.
17178 Dec. 13, 1910. (125)	53 years. White. 7 preg.; menopause 9 years ago. Irregular bleeding for 1 year.	Path. No. 13816. Squamous cell carcinoma.	Curettage and cauterization 2 days before; wide abdom. operation. Prognosis, fair.	Cystitis. Disch. Jan. 17, 1911.	Recurrence April, 1911.
17182 Dec. 17, 1910. (126)	46 years. White. 4 preg. Irregular bleeding for 5 months.	Path. No. 13807. Adeno-carc. cervix extending into fundus.	Wide abdom. operation; resection and implantation of left ureter.	Disch. Jan. 28, 1911.	Death, July, 1911, from recurrence.
17485 May 6, 1911. (127)	41 years. White. 5 preg. Slight bleeding for 7 months.	Path. No. 14220. Squamous cell carcinoma.	Cauterization 3 days before; wide abdom. operation. Prognosis, good.	Entire incision opened spontaneously. Disch. June 13, 1911.	March, 1913: In excellent health.
17548 June 14, 1911. (128)	56 years. White. 10 preg.; menopause 4 years ago. Irregular bleeding for 4 months.	Path. No. 16363. Squamous cell carcinoma.	Cauterization 2 weeks before; wide abdom. operation; advanced case.	Vesico-vag. fistula on 4th day. Disch. July 15, 1911.	March, 1913: No recurrence; splendid health.
17560 June 25, 1911. (129)	54 years. White. 1 preg.; menopause 5 years ago. Irregular bleeding for 5 months. Hg. 79.	Path. No. 16323. Squamous cell carcinoma.	Cauterization; wide abdom. operation; very advanced case.	Vesico-vag. fistula 10th day. Disch. July 18, 1911.	Died April, 1912, from recurrence.
17597 June 28, 1911. (130)	45 years. White. 8 preg. Irregular bleeding for 2 months with severe pain over abdomen.	Path. No. 16391. Squamous cell carcinoma. Metastases to ovary.	Prelim. cauterization; wide abdom. operation; advanced case.	.....	Death on 6th day from peritonitis.
17735 Aug. 22, 1911. (131)	45 years. White. 5 preg. Blood-tinged leucorrhoea for 4 months. Hg. 7.	Path. No. 16650. Squamous cell carcinoma.	Cauterization 2 weeks before; wide abdom. operation; very advanced case.	Recto-vag. fistula. Disch. Oct. 14, 1911.	Recurrence within a few weeks.
17750 Sept. 9, 1911. (132)	28 years. Colored. 7 preg. Irregular bleeding for 8 months. Hg. 38.	Path. No. 16655. Squamous cell carcinoma.	Prelim. excision for diagnosis; wide abdom. operation. Prognosis, good.	Disch. Sept. 26, 1911.	Feb., 1912, in good health.
17778 Sept. 12, 1911. (133)	58 years. White. 4 preg.; menopause 8 years ago. Profuse vaginal disch. for 2 years.	Path. No. 16654. Squamous cell carcinoma.	Cauterization; wide abdom. operation.	Disch. Oct. 26, 1911.	Not located.
17804 Oct. 20, 1911. (134)	48 years. White. 3 preg.; menopause 2 years ago. Blood-tinged leucorrhoea for 5 months; severe abdominal pain for 6 months.	Path. No. 16700. Squamous cell carcinoma.	Prelim. cauterization; prelim. cath. of rt. ureter; wide abdom. operation. Prognosis, fair.	Vesico-vag. fistula on 16th day. Disch. Nov., 1911.	April, 1913: Enjoying the best of health; no recurrence, 1912.
18026 Dec. 2, 1911. (135)	41 years. Colored. 6 preg. Irregular bleeding for 6 months.	Path. No. 16847. Adenocarc. cervix.	Cauterization; wide abdom. operation. Prognosis, fair.	Death 20th day; pulmonary embolism.	
18060 Dec. 6, 1911. (136)	57 years. White. 4 preg.; menopause 8 years ago. Irregular bleeding for 2 months.	Path. No. 16844. Squamous cell carcinoma.	Cauterization; wide abdom. operation. Prognosis, very bad. Incomplete.	Disch. Dec. 22, 1911.	Recurrence 1912.
18083 Dec. 16, 1911. (137)	45 years. Colored. 4 preg. Profuse watery lower abdominal flow for 4 weeks.	Path. No. 16880. Squamous cell carcinoma.	Cauterization; wide abdom. operation; advanced case.	Disch. Jan. 9, 1912.	Not located.

## FURTHER ANALYSIS OF THE SUCCESSFUL OPERATIONS FOR CARCINOMA OF THE CERVIX.

Clinical No.	Serial No.	Path. No.	Length of time since the operation.	Clinical No.	Serial No.	Path. No.	Length of time since the operation.
Years. Months.				Years. Months.			
7927	2	3904	11 11	14325	86	12300	5 4
8199	4	4222	11 1	14557	87	12340	5 1
8278	10	4977	10 2	14911	82	12630	4 1
9228	13	5436	10 3	15053	84	12920	4 2
10324	25	6443	7 11	15406	96	13370	4 1
10444	27	6680	9 11	15977	103	14117	2 1
10605	21	6857	8 8	16112	105	14207	2 1
10627	33	6885	7 4	16152	107	14418	1 1
11225	37	7467	9 9	16176	108	14378	1 1
11233	39	7691	7 8	16661	115	15062	2 1
11390	48	7997	7 10	16757	117	15207	2 1
12397	58	9362	6 1	17485	127	16250	1 1
29944	57	9812	5 10	17549	128	16363	1 1
29887	60	10212	5 8	17769	132	16652	1 1
14063	71	11854	5 7	17894	134	16716	1 1
14129	77	12001	3 7				

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## A BRIEF HISTORY OF THE METHODS OF RESUSCITATION OF THE APPARENTLY DROWNED.\*

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Among the various institutions that have been formed for the welfare of mankind, none appear more worthy of our attention than those that are calculated for preserving the human species. In the vast realm of human endeavor perhaps no body of men have been more instrumental in inaugurating a world-wide movement which had for its sole purpose the saving of human life than was the society at Amsterdam, instituted in the year 1767, for the recovery of the apparently drowned.

In the spring of that year a few wealthy and benevolent gentlemen of the City of Amsterdam, struck with the variety of instances in which persons falling into the water were lost for want of proper treatment when brought on shore, formed themselves into a Society for the Recovery of Drowned Persons. From a careful search through the literature, I find that this institution was the first of its kind ever organized, and we shall see later that it became the parent of innumerable similar institutions scattered through the world.

The methods employed in the resuscitation of drowned persons previous to the establishment of this institution, and also those recommended by this society, were based almost wholly upon empiricism, and it was not until some years after the founding of the Royal Humane Society in London, in 1774, that any systematic study was made to disclose the rationale underlying the various methods which were then in use.

The members of the Amsterdam Society pursued their design with so much zeal and success that, in the space of four years, they had the satisfaction to find that, in not less than 150 cases, drowned persons were recovered by the means pointed out and recommended by them in the United Provinces by advertisements and other publications. Their *first* object was to inform the common people, as well as the inferior practitioners of physic, in what manner to treat a person apparently lifeless; and their *second* was to animate them by proper rewards to pursue the methods recommended.

The general instructions published by this society are very interesting. They tell us that

As soon as the drowned body was found, it was to be conveyed, extended upon a hand-barrow, a ladder, or some long board, to a barn, a shed, or other place under cover, where no house was near enough for its reception. Then it was to be laid out upon a table or bench, in a sloping position, the head higher than the feet; it was then to be stripped, laid in a blanket, and carefully examined to see whether any parts were injured.

The bodies of drowned persons, since they were generally found wet, cold and stiff, were to be immediately well dried, placed in a temperate air, and rubbed with dry and warm flannels or a flesh-brush. If dry rubbing did not soon prove efficacious, then some spirits or coarse salt were to be sprinkled upon the parts and the rubbing resumed; the spirits thus used were the volatile spirit

of sal ammoniac, or hartshorn, or *eau-de-luce*, mixed with brandy, rum or malt spirits. The parts to be rubbed with steadiness were the back-bone, the sides of the body, the abdomen and breast, the palms of the hands and soles of the feet; other parts to be chafed with the above-named spirits were the temples, ears and neck. These spirits were not to be applied in profusion.

Since the mouth and nose of drowned persons were often filled with mud or froth, this was to be cleared away with a goose-feather, or by repeated injections of some lukewarm water, tea or aromatic infusion—the body to be laid upon its side, that the liquid might run out.

If a small degree of heat was obtained from the rubbing alone, a recovery then became very promising, and the body was then to be laid in a blanket (or in a bed where it could be had) between two healthy persons, undressed, who were to continue rubbing and gently agitating the body, to increase the heat to a natural state. But if the first degree of heat was not produced by the diligent rubbing, then dry heat was to be added, in bed if possible, by some bottles filled with hot water, and wrapped up in flannel; heated tiles or bricks, so wrapped up, but used with precaution; also hot sand in bags, laid near, but not to touch, the sides, the hands and the feet; and a number of cloths, alternately heated, were to be placed especially about the head, the neck and the coldest parts of the body and renewed as they cooled.

The introduction of air into the body was also warmly recommended. It was practised in two different ways and tended "to blow up the lungs to renew the circulation or to swell the intestines to produce motion." The attempt to fill the lungs was made by the nose, and required a particularly constructed pipe, one end of which fitted the nostrils and the other received the nozzle of a small, clean bellows that was to be worked cautiously and slowly, while the mouth was kept closed and the throat gently pressed back to make the air take its right course down the windpipe and not into that which leads to the stomach. The directions stated that when this operation was well performed it might prove of great benefit, but that it was difficult and without the pipe was scarcely practicable. Further, if the bellows were not at hand, the trial was not to be made with the breath of the operator, which "has become noxious and unfit to enter any lungs again."

The other method was made by the fundament, in which case the bellows could be more easily applied. This latter method was much more frequently used, and it was strongly advised that when common air did not suffice to bring about some signs of life a more stimulating vapor was to be blown up the intestines, such as "the smoke of tobacco for strong bodies, or some aromatic herb, as sage, mint or rosemary, for the weaker sort." It was accomplished as above mentioned by the use of bellows or the so-called fumigator—the operation being commonly spoken of as fumigation. When a fumigator was not at hand, it could be performed very satisfactorily by the use of the common smoking-pipe filled and lighted, the bowl of which was put into a common clyster-bag; or by two

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pipes inverted on each other, and held together by a piece of strong paper, or joined by a kind of tinder-barrel. In the words of the translator,

While the air, vapor or smoke is being introduced into the body, the belly must be gently moved and pressed upward with the hand; and the operation must be repeated and continued for a length of time until signs of life appear. When those are obtained, attention is then required, to go on slowly, and to give heat and motion by degrees but not to overpower, by hasty endeavors, a body then in so weak a condition as to be hurt by every inconsiderate attempt. It should at that time be kept in gentle agitation, by means of the blanket upon which it lies. The nostrils and throat are to be tickled with a crow feather; and powders or salts that provoke sneezing may then be used. The temples, ears and neck are to be chafed with the volatile spirits above mentioned, mixed with brandy or common spirits; some raisin-wine, tincture of castor or peppermint water, or other cordial, ought then to be put into the mouth, by slow degrees, a teaspoonful at a time, and allowed to go down before another is given.

Keith, in his lectures on artificial respiration, remarks that mouth to mouth inflation, a form of artificial respiration, was also somewhat extensively used. The case reports certainly substantiate this statement, though Dr. Johnson, of London, in his account of the Amsterdam Society published about 1785, registers an objection against the method, as I have stated above. In the performance of this method the operator closed the patient's nostrils and applied his mouth to that of the patient and inflated the lungs and expanded the belly and chest. By compressing these parts with his free hand, the operator brought about an expiratory movement. It is most likely that this method had been used for several centuries, though perhaps it was not so often employed by the common people prior to the foundation of the Royal Humane Society.

Regarding the advisability of *venesection* as an aid in resuscitation, I find that there was considerable difference of opinion as to its usefulness, but on the whole most authorities seriously questioned its efficacy; and especially was this true in England during the last two decades of the eighteenth century. The experimental work of A. Fothergill, John Hunter and others clearly demonstrated the ineffectiveness of this method of resuscitation, particularly when practised by the well-intentioned but ignorant laymen, which was only too frequently the case. It was, however, undoubtedly recommended by the Dutch society, though I am unable to substantiate the statement from a perusal of the literature. The reason for such an opinion is the fact that out of sixty cases reported by the Dutch institution and republished later by Johnson, bleeding was attempted in more than 75 per cent of the cases; and quoting from Keith, it was "particularly necessary as life returns."

The society further recommended the use of *emetics* and *stimulants*, both internal and external, as accessory and useful means.

A survey of the case reports shows quite conclusively that various other methods of resuscitation than those I have mentioned had been used by the laity of both England and Europe from very early times. Most of them, however, were crude, dangerous and inefficient. The so-called "*barrel method*" had

been practised for many years, and especially among the sailors. In this method the body was simply placed upon the barrel, face downwards, the legs of the patient being grasped by the physician or other assistant and raised to the horizontal, and the body was then rolled forward and backward. If we carefully inquire into the principles underlying this method, we find that it has much in common with a method recently advised by Prof. Schäfer.

*Suspension by the heels, or inversion of the body*, and merely *rolling the body on the ground* were other methods occasionally employed.

In summary then we may remember the following methods used in the resuscitation of the apparently drowned, possibly before and certainly during the last half of the eighteenth century, and recommended by the Amsterdam Society:

- (1) Friction and rubbing of various parts of the body with or without stimulants.
- (2) Warmth, in the form of dry heat, or even the "warm bath" in some instances.
- (3) Fumigation.
- (4) Gentle agitation of the body.
- (5) Artificial respiration by bellows and mouth to mouth inflation.
- (6) Venesection.
- (7) Emetics and stimulants.

Especial importance was placed upon friction, warmth, and fumigation as the most satisfactory and successful of the methods.

The society placed no definite limit upon the time for the continuance of the necessary treatment in any given case; it was to be persevered in, without discouragement, till life be recovered; or till it was plainly evident, from a very long train of fruitless endeavors, that no kind of change was obtained. But the space of six hours or more should at least be occupied to obtain the first sign of life.

I should like to read you the reports of a few of the cases successfully recovered, as they have been translated from the memoirs of the Dutch society. They are indeed interesting and clearly illustrate the methods employed prior to the beginning of the last century.

CASE 14.—At Amsterdam, on the 25th of February, 1769, a maid servant, drawing water in the morning, fell into the canal before her master's door, and after some struggling sank to the bottom. She was got out, in about a quarter of an hour, and had not the least sign of life in her. Air and tobacco-vapor were immediately blown up her intestines; she was stripped, was laid before a fire, and was rubbed with cloths dipped in brandy, till some signs of life were discovered, when also some froth appeared upon her mouth. An assisting surgeon's apprentice tried to bleed her, but got no more than a few drops; not being satisfied with this, he opened the jugular vein, and took away eight or nine ounces of blood. As she recovered, fourteen or fifteen drops of spirits of sal ammoniac were given her in water. Some hours afterwards she was put to bed, was rubbed, and had a tobacco-clyster. She was also bled in her right arm, and at length came entirely to herself, yet complained of an oppression in her breast. At noon she was ordered to be bled a third time. At four in the afternoon, little complaint

remained, but a straitness over her breast, which she had before been subject to, and was afterwards cured.

CASE 15.—At Rotterdam, on the 8th of April, 1769, the daughter of Meindert den Broeder, a girl of ten years of age, fell into a stagnant pool, near the rampart of the town, and stuck in it for some time. When she was taken out of it, she seemed, according to the account of the surgeon Hooykass who directed the following treatment, to be absolutely dead, and looked as black as if she had been hanged, having also a quantity of froth at her lips and nose. She was immediately stripped, put between warm blankets, and rubbed. After the introduction of some tobacco-vapor into the intestines, a bleeding was attempted, and only about four ounces of blood obtained, by drops; the jugular vein not being practicable, upon account of the great swelling of the neck and head. Three persons then continued to rub, and inject smoke, for the space of an hour, when a faint yawning, like that of a departing patient, gave the first small sign of life. Some spirit of sal ammoniac, held to the nose, produced no effect; but in an hour and a half some slight pulsation was discovered; soon after which, she discharged upwards and downwards, and then began to move her legs and arms. At the end of two hours, she began to scream, and cried out, "I am fallen into the water"; and afterwards complained of soreness all over her body. Some cordial was at this time given her, which had before been fruitlessly attempted, and now served greatly to recover her. About an hour and a half afterwards, she complained of a great pain in her bowels, and a difficulty in breathing, for which a clyster with an infusion of tobacco was administered, and it operated in so copious a manner as to give her great relief. An hour and a half after this, she was delirious, and still more oppressed. It was again tried to bleed her, and still without success; but a blister was applied to her back, and was thought to do her good. A laxative medicine was given her by degrees during the night, and had its intended effect. Next morning she had a violent pain in her side, and a considerable oppression, for which recourse was had to bleeding, which at last succeeded on her hand, and immediately relieved her. The next day she voided some hard, black, clayey stuff; the day after that, she complained of a pain in her breast, which was found to proceed from some skin being rubbed off during the operation. Her tongue remained furred for some days, but was at last cleared by a repetition of the laxative medicine; and she then gradually recovered her former strength, to the great comfort and assistance of an old, helpless father, whom this girl took care of, whilst the mother was absent, indefatigably working as a char-woman for the subsistence of her family.

CASE 17.—At Amsterdam, on the 17th of April, 1769, Anna Woertman, a woman of 27 years of age, belonging to that pleasant part of the city called the Plantage, was taken out of the water without its being known how long she had lain in it. She was inconsiderately rolled upon a float, for a quarter of an hour, and is said to have voided a good deal of water. She was then carried into a house, where Bernardus Donselaar, an apothecary, was sent for, and told she had just before given some very faint sign of life, though in fact she appeared quite lifeless, was stiff, and had green and blue spots all over her body. She was laid before a fire in blankets, and was rubbed with a mixture of spirit of sal ammoniac and essence of rosemary, along the backbone, the loins, the neck, the head and the temples; and a stone jug filled with hot water was laid at her feet. Some farther signs of life then appearing, she began to shake as in the cold fit of an ague, spoke and complained; upon which some spoonfuls of Geneva were given her, and she was blooded. Her blood was black and thick, not inflamed. As she was thirsty, some milk and water was given her; and then she fell into fits seemingly strong enough to carry her off; these, however, were removed by a cordial administered to her. In the space of four hours and a half she was so

much better as to be carried home, and put to bed to her sister, where she fell into a breathing sweat. About five hours afterwards she complained of a great oppression, and a violent pain in all her limbs; for which an aperient laxative mixture was given, which made her part with a quantity of watery matter. The pain augmenting, and fixing in her side and breast, she was twice bled; and her blood being then found much inflamed, it was wished to repeat the bleedings; but she proved to be too weak. However, a blister was applied to her side; and other treatment being opportunely given, she was entirely recovered in the space of a fortnight, the slowness of which is attributed to her having been afflicted six months before with a fever, and to constant depression of spirits, upon account of bad circumstances.

CASE 19.—At Amsterdam, on the 29th of July, 1769, a boy of 14 years of age, called Jacob Voorn, rowing with some others in a boat, fell overboard, and sunk directly. More than 20 minutes elapsed before he could be got out of the water. He was then carried into a house, where, by the direction of Floris Loosjes, an apothecary, he was stripped of his clothes, laid in a blanket, and rubbed all over; tobacco-smoke was blown up into his intestines, and wind forced into his mouth, whilst his nose was held closed; and this was repeated. He was bled at the arm, and nine or ten ounces of blood were taken away; after which, upon the appearance of some signs of life, a little brandy was put into his mouth; and the room in which he was thus treated, being thought too close, he was carried into a more airy room, where, some more brandy being forcibly spouted into his throat, he roused at once, and screamed out. When he became quieter, some milk and water was given him to drink. He was then put to bed, had hot cloths applied to him, and was well covered up. He grew warm by degrees, excepting at the soles of his feet, and was delirious at times; but that ceasing, he complained of a pain and inflammation in his throat, which, by the prescription of a physician, was got the better of in a few days, and the lad was totally restored.

The establishment of this Dutch institution was speedily followed by apparently great success, and the advantages accruing from it to the state induced each of the several provinces of the republic to take proper measures for extending its benefits, by enjoining an observance of the society's directions through their respective districts. Further, the assiduous endeavors made to spread the knowledge of this practice caused its reception and led to the forming of similar institutions in the following countries and cities. From the city of Amsterdam, in Holland, where it took its origin and whence it soon became known throughout the republic and the Netherlands, it found its way southward into Italy, and was received by the boards of health of Venice, Milan and Padua. The King of Naples ordered it to be connected with the purposes of the great infirmary in his capital; his majesty's example was followed in the cities of Florence, Leghorn and Genoa. It was further encouraged by the regency of Hamburg, whence it passed through Germany. The Empress Queen of Hungary gave it protection and directed it to be made known in her extensive dominions, and so it spread throughout all the countries of Europe.

Having briefly considered the methods of resuscitation which were in use upon the Continent during the latter part of the eighteenth century, let us now direct our attention to Great Britain and learn what was the condition of things, relative to our subject, present in that country.

You will recall that the Amsterdam Society was established

in 1767. It was but six years later that we find an Englishman—a Dr. Cogan, a learned and judicious physician of London—had become interested in this Resuscitative Movement, so to speak, and it was in the year 1773 that this gentleman translated the Memoirs of the Dutch Society. This booklet immediately arrested the attention of one of the most remarkable men of London, Dr. William Hawes, and the latter tells us that it was Dr. Cogan who first fired him with the purpose of introducing into London the methods practised by this Amsterdam institution. His one object was to allure the advocates of humanity and of science to the discussion and investigation of this very important cause, and we need not go far to find that his purpose was completely realized. Thus, this resuscitative movement, as we may now call it, reached England in 1773 in the persons of Dr. Cogan and Dr. Hawes.

On the 18th of April, 1774, in the London Coffee House, these two men and a score or more of other friends founded the Royal Humane Society. It is of historical interest to recall that such names as David Garrick, Oliver Goldsmith, John Hunter, A. Fothergill, Frederick Bull, Lord Mayor of London, James Horsfall, Heberden, Lettsom, Beaumont, Parkinson and many others appear in the Transactions of this society as officers, members and supporters. Dr. Hawes and Dr. Cogan were the institutors of the society and the former was its leading spirit until his death in 1808.

I think we may say with all truthfulness that the early history and development of the methods of resuscitation are in reality the history and development of this institution. It was through its influence that the problems surrounding the resuscitative art were thoroughly, systematically and scientifically investigated, and through these researches a great many facts of scientific and practical value which had hitherto been inexplicable came to be common knowledge.

The methods advocated by this English society were similar in many respects to those recommended by the Dutch institution. Their directions stated that the restoration of heat is absolutely essential to life, and therefore they emphasized particularly the application of warmth. Artificial respiration and especially fumigation were quite extensively used in the manner described above. Agitation was similarly recommended. "One or more persons should take hold of the legs and arms and vigorously shake the body, which procedure could be repeated by the assistants several times within the hour, if necessary." They further directed that if one hour had elapsed, "and there be no signs of animation, and any brewhouse or bakehouse be in the neighborhood, the body should be placed in warm grains, or ashes, little exceeding that of healthy persons. If so fortunate as to obtain a warm or vapor bath, it should be employed in conjunction with the other modes of resuscitation."

In addition to the Dutch methods, the society stated that electricity would increase the beneficial tendency of the restorative means. "The electrical shock," says Mr. Kite, "is to be admitted as the test of any remains of animal life; and, so long as that produced *contraction*, the person may be said to be in a *recoverable* state; but, when that effect has altogether ceased,

there can no doubt remain of the party being absolutely and positively dead." Dr. A. Fothergill observed, "where the vital organs are sound and only their *motion* suspended, why not have immediate recourse to the most *potent stimulus* in nature, which instantly pervades the inmost recesses of the animal frame? Why not immediately apply *electrical shocks* to the heart and brain, the grand sources of motion and sensation of the animal machine?"

*Venesection*, though it was frequently used by physicians and others in their attempts at resuscitation, was strongly opposed by the Royal Humane Society.

Upon the solicitation of the officers of the society, and especially of Dr. Hawes, many investigations were made by the most renowned scientific men of that day to determine the efficacy of the various treatments then employed, and it was also hoped that from the results of their work new methods, simpler and more effective, might be discovered. Within the next twenty-five of thirty years numerous monographs appeared regarding the effectiveness of the various methods employed for restoring drowned people. It is quite beyond the limits of this paper to enter into any detailed analysis of these various experimental data, and I shall venture to give you a very brief résumé only of the more important of these contributions.

It was indeed a circumstance of no small triumph to the Royal Humane Society, that the practicability of the resuscitative art, obtained by its exertions, first drew the attention of these great men to investigate its theory.

In 1776 Dr. William Cullen, Professor of Physic at the University of Edinburgh, upon the solicitation of Dr. Hawes began his experimental study. This gentleman begins his judicious publication by defining "*The Vital Animal Principle*," which he makes to consist in "that disposition or condition of the nerves and muscular fibers, by which they are rendered susceptible of irritability and sensibility, conjoined with a due organization of the parts." It seemed to him, therefore, a fair and reasonable inference to draw this conclusion: that the action of the heart and lungs, the circulation, and consequently all the functions of life, though they have long ceased, may be restored. The numerous and well-attested facts of persons recovered, who had for a long time exhibited "all the exterior signs of death," he thought, corroborated the validity of this opinion.

The author proceeds farther to observe that, as dissections show that seldom either the lungs or the stomach in drowning receive so much water as could possibly injure the system, it is probable that the death, which ensues or seems to ensue, is entirely occasioned and owing to respiration being interrupted, and the circulation of the blood, in consequence, ceasing, whereby the body very soon loses its "*natural heat*," and the "*vital principle*" therewith its activity.

If there can be means found to restore this "*natural heat*" and "*vital activity*," there will be a possibility, and almost a certainty, of restoring drowned persons. The results of his experimental work led him to recommend warmth as probably the most efficacious means. He also advised stimulants per



anum—preferably tobacco-smoke—inflation of the lungs . . . use of the bellows, blood-letting and emetics.

A few years later John Hunter investigated the subject. His researches dealt chiefly with the influence of the lungs upon the heart. This ingenious physiologist begins by dividing violent deaths into three kinds:

First, when a stop is put to the action of life in the animal, but without any irreparable injury to a vital part.

Second, where an injury is done to a vital part.

Third, where absolute and positive death instantly takes place in every part.

He was of the opinion that drowning most commonly comes under the first; and upon that basis he professed principally to consider the subject of the drowned.

Hunter further observes that *privation of breathing* appears evidently to be the *first cause of death*, and the *ceasing of the motion of the heart*, the *second or consequent*. He therefore argues that most probably the restoration of the pulmonary action is all that appears necessary to restore the motion of the heart; for, if sufficient life still exists to produce that effect, we may reasonably suppose every part equally ready to move, the very instant the *action of the heart* takes place, their actions and motions depending so much upon it. Mr. Hunter attempts an illustration of the propriety and justice of this conclusion by considering what happens at the birth of children, when too much time has intervened between the interruption of that life which is peculiar to the foetus and that which depends on breathing. In such cases, there being a total suspension of the actions of life, the child remains to all appearances dead, and would certainly die if air were not thrown into its lungs, and by such means the first principle of action restored.

To the same purpose the author quotes the results of one of his earlier experiments upon dogs. He constructed a pair of double bellows and connected it to the dog's trachea in such a manner that he could by one action throw fresh air into the lungs, and by another suck out again the air which had been thrown in by the former, without mixing them together. By working the bellows the dog was kept perfectly alive. While the artificial respiration was going on, the dog's sternum was taken off, and the lungs and heart exposed; the heart continued to act as before, only the frequency of its action was considerably increased. The motion of the bellows being stopped, the heart became gradually weaker, and less frequent in its contractions, until it ceased entirely to move. By renewing the action of the bellows the heart again began to move, at first very faintly, and with long intermissions; but by continuing the artificial breathing, its motion became as frequent and as strong as at first.

Mr. Hunter repeated this experiment ten or twelve times, sometimes stopping for five, eight, or ten minutes. Every time he left off working the bellows, the heart became extremely turgid with blood, the blood in the left side becoming as dark as that in the right, which was not the case when the bellows was working. He considered the animal to exhibit exactly the same conditions here as in drowning. He concluded that what the drowned person needed most of all was air, fresh air, and

what was still better, the so-called *dephlogisticated air* or oxygen, which had but recently, 1774, been discovered by Priestly and Lavoisier.

The results of further experimental work led him to recommend, in addition to artificial respiration by bellows, etc., warmth, stimulants, forced movements and electricity. He was one of the few strong opponents to the use of tobacco-smoke as an efficacious means of restoring the apparently drowned, and likewise condemned the use of the lancet and emetics.

In 1781-85, Dr. A. Fothergill undertook experimental investigation, and his recommendations were in the main quite similar to those of Hunter. He observed that in all cases of suspended animation the grand intention of the operator should be to excite the latent principle of irritability, on which the motion of the vital organs immediately depends. Although this principle remains a considerable time after the lungs are quiescent, yet it never can be restored to its activity until that organ is again put in motion. His experience showed that this could be often effected by blowing air into the windpipe, and that renewing pulmonary action was one great step toward restoring the energy of the heart, the brain, and the arterial system, and consequently of the other subordinate springs of the animal machine. He was convinced that inflating the lungs was probably one of the most efficacious methods of restoring animation; and he felt that dephlogisticated air was undoubtedly more serviceable than ordinary air.

The other improved methods which he ventured to suggest were the "electrical shock" and heat; and these, together with oxygen, were in his opinion the most powerful agents in nature that should be employed in the resuscitation of the drowned.

Regarding electricity he writes as follows:

Whoever considers its effects in increasing the action of the heart and arteries, in accelerating the circulation of the blood, and consequently in promoting the progressive motion of all the animal fluids, will scarcely hesitate to acknowledge it as a suitable agent for restoring suspended animation.

In his dissertation on "Heat—Its Efficacy in Restoring Animation," we find this interesting paragraph:

When the warm bath cannot be speedily procured, a *partial application* of heat may prove very beneficial. Hence a warm sunshine has, more than once, afforded a useful auxiliary on these occasions. This circumstance might be improved, when the weather is favorable, by collecting the solar rays in the focus of a lens or speculum, and directing them with more or less intensity upon different parts of the body. By thus directing the concentrated rays, with due caution, on the eye, the pupil would not fail to contract, if the muscular fibres of the iris retained even the smallest degree of irritability. Might not this mode of application afford a method of discovering whether any remnant of life yet remained in the other parts of the body, and lead us to a new criterion between real and apparent death?

A. De Haen, Professor of Medicine in Vienna, did important experimental work on dogs. These experiments were concerned chiefly with the drowning and subsequent resuscitation of the animals. He was probably the first to state the fact that water entered the lungs during drowning, and he therefore recommended the inversion of the body and other means for

expressing the water from the lungs, in addition to the other methods already in use.

E. Goodwyn, experimenting about 1782, was the first to discover that the tongue might fall back and thus occlude the opening into the larynx.

It is interesting to trace the fate of some of these various methods of resuscitation; for example, the use of the bellows. This method had long been in use by anatomists and physiologists in keeping animals alive during experiments, and it appears to have been first used on a human being by Dr. John Fothergill, of London, about 1750. It is also known to have been employed by the laity during the middle part of the eighteenth century. The bellows was first recommended by the Royal Humane Society in 1782 and for some 35 or 40 years no word was registered against it. It was Leroy of France who, in 1829, showed that it was possible to kill an animal by suddenly inflating its lungs and also to produce emphysema of the lungs and pneumothorax in dead animals. He found that from 20 to 80 mm. Hg. pressure was sufficient. The fact which damned the use of the bellows was Leroy's statement that the lungs of those on whom inflation had been unsuccessfully performed were frequently emphysematous. It was not until the publication of Paltauf's memoir in 1888 that emphysema was recognized as a consequence of drowning. As a result of Leroy's statement the use of the bellows fell into disgrace as a method of resuscitation.

Sir William Brodie was also instrumental in relegating the bellows to the past. In 1821 he stated dogmatically that there were few cases of drowning in which artificial respiration would prove of any service. His reason was that in from two to three minutes after respiration had ceased, the heart stopped, and when that occurred artificial respiration was powerless to restore it. It was of use only when it could be applied before the heart had stopped, and such cases generally recovered without assistance.

Because of these statements and Leroy's work, artificial respiration was regarded as an altogether secondary measure in the restoration of the drowned.

The history of the method of fumigation illustrates how quickly and how unreasonably a method at one time extensively used may fall into disrepute. It was undoubtedly used for many years before the foundation of the Royal Humane Society, and was employed successfully for some 35 years following the organization of this institution. Three experiments conducted in 1811, by Brodie, then only about 28 years old, brought the practice to an abrupt close. He discovered that four ounces of a strong infusion of tobacco injected into the intestines was sufficient to kill a dog in from eight to ten minutes, and that one ounce could kill a cat. Nicotine was a cardiac poison. During the previous 35 years the method had been found to succeed in hundreds of cases and had been warmly recommended by such authorities as Cullen, Cogan, Ward, Dixon and Hawes. Three crude experiments by a young surgeon were sufficient to overturn 35 years of experience.

We now come to what may be designated as a new era in the resuscitative movement. I refer to the introduction of

*mechanical expansion and compression of the chest wall* as a new method in recovering the apparently drowned. Dr. Marshall Hall was really the founder of this method, though artificial movements of the chest had been intentionally practised before this time. It was Leroy of France, in 1829, who observed that the bellows, in the hands of an ignorant operator, might become a dangerous weapon and proposed in its stead a method of artificial respiration quite like that introduced by Howard some 40 years later. This method consisted in laying the patient face upwards and compressing the anterior wall of the abdomen and thorax, thus producing expiration, inspiration resulting from the elastic rebound of the chest wall.

The first systematic attempt to deal with this subject, however, was that of Dr. Marshall Hall, of England. In 1857 this learned physiologist published his paper entitled, "Prone and Postural Respiration in Drowning." The method is known as the Marshall Hall or the *ready* method, the latter proposed because no apparatus of any kind was required.

Hall carried out a series of very ingenious experiments, from which he concluded that the condition of drowning was one of anæsthesia and poisoning by a surcharge of carbon dioxide. He also found (as Goodwyn had pointed out 70 years before) that when the patient was supine the tongue and larynx were apt to fall back and occlude the air-passage. When the patient was placed in the prone position, this difficulty was avoided. Briefly, his directions were as follows:

(1) Treat the patient *instantly, on the spot, in the open air*, freely exposing the face, neck and chest to the breeze, except in severe weather.

(2) Send with all speed for medical aid, and for articles of clothing, blankets, etc.

(I) To clear the throat:

(3) Place the patient gently on the face, with one wrist under the forehead. (All fluids and the tongue itself fall forward, and leave the entrance into the windpipe free.)

(II) To excite respiration:

(4) Turn the patient slightly on his side, and

(a) Apply snuff or other irritant to the nostrils, and

(b) Dash cold water on the face, previously rubbed briskly until it is warm.

If there be no success, lose no time, but—

(III) To imitate respiration:

(5) Replace the patient on his face.

(6) Turn the body gently, but completely, *on the side and a little beyond*, and then on the face, alternately, repeating these measures deliberately, efficiently, and perseveringly, 15 times to the minute *only*.

(7) When the prone position is resumed, make equable but efficient *pressure along the spine* and lower thorax, removing immediately before rotation on the side.

(IV) To induce circulation and warmth:

Continuing these measures,

(8) Rub the limbs *upwards*, with firm pressure and with energy, using handkerchiefs, etc.

(9) Replace the patient's wet clothing by such other covering as can be instantly procured.

From time to time—

(V) To again excite inspiration:

(10) Let the surface of the body be slapped briskly with the hand; or

(11) Let cold water be dashed briskly on the surface, previously rubbed dry and warm.

Hall strongly advised against the removal of the patient, as involving dangerous loss of time; against the use of the bellows, or any forcing instrument, and the warm bath, stating that they were positively injurious. Galvanism and the inhalation of oxygen he regarded as useless. The inhalation of ammonia he thought might be of some value.

In analyzing this method, we find that the essence of it consists in altering the position of the patient from a lateral to a prone posture, the supposition being that with these changes in the position of the body alterations would be produced in the capacity of the thorax, the front of which, in the prone position, would sustain the weight of the trunk and would thus be somewhat compressed, while in the lateral position the more movable front of the thorax would be relieved of pressure and would tend to resume its original volume by virtue of its elasticity. It should be added that the weight of the trunk is, in this method, assisted in the task of forcing air out from the thorax by pressure between the shoulder blades and over the lower chest when the body is in the prone position, and it may further be added that this pressure tends considerably toward the efficiency of the method. The gaseous exchange effected by this method was found to vary from 70 cc. to 240 cc.

The records show that this method was followed with great success for many years. It was adopted in England by the Royal Humane Society and by the National Life Boat Institution and was, and still is, taught and practised by both these bodies, and has also, until lately, been the common method employed in the Royal Navy.

In the following year, 1858, Dr. H. R. Silvester worked out a method of artificial respiration on quite a new principle. His aim was to imitate as nearly as possible the natural movements, and especially the raising of the ribs. He selected the supine posture. His experiments were conducted upon the dead body. With the object in mind of raising the ribs, he advocated the pulling of the arms forcibly above the head, thereby dragging upon the ribs by means of the pectoral and other muscles passing between the arms and the thorax, and so effecting an enlargement of that cavity by the elevation of the ribs. Expiration in this method is brought about by lowering the arms again to the sides and then compressing the thorax laterally. By this mechanism it was conceived that a large amount of air-exchange might be obtained, and most experimenters agreed that the Silvester method was the most effective one in producing an ample ventilation of the lungs. A respiratory tide varying from 300 cc. to 500 cc. could often be produced, but it was a laborious method and effective only when applied expertly.

Both this and the method of Marshall Hall were submitted in 1862 by the Royal Medical and Chirurgical Society to the investigations of a committee which made a number of experi-

ments upon the cadaver. As a result of their report (which was quite inconclusive), however, the Silvester method was put in the first place by the Royal Humane Society and was adopted as an alternative method by the National Life Boat Institution. It was also taught, along with others, by the Royal Life Saving Society, when that society was established in 1891, and it has now for many years been the method chiefly employed in Great Britain and in many parts of Europe for the resuscitation of drowned persons.

In 1869, Dr. Benjamin Howard, of New York, published the description of another method, which depended, not upon traction or posture, but upon pressure alone. In his plain rules Dr. Howard first instructs you to turn the patient face downward and press two or three times with all your weight upon the back, so as to press the water out of the lungs and stomach; then to turn the patient face upward and (after producing over-extension of the spine by placing a support under the patient, so as to make the subcostal margin prominent) kneel over the lower part of the body, placing a hand over each prominent subcostal margin so that the fingers occupy the furrows between the ribs above the margins, the palms below them. When pressure is applied by the operator placing his weight over his hands, expiration is produced by a triple movement; first, the lower six ribs are depressed; second, the abdominal contents, especially the liver and spleen, are compressed so as to force upwards the diaphragm and empty the lungs; and third, the extension of the spine is partly undone. The pressure is relieved by a sudden jerk backwards, and the spine again becomes overdistended, the lower ribs again become prominent, and the viscera slowly return to the position of rest. Inspiration is thus effected by the rebound. This operation is to be repeated from 10 to 12 times per minute.

This method differs from the Marshall Hall method, not only in employing pressure as the main active agent in effecting air exchange, but also in the position of the body. In this respect the Howard method resembles the Silvester method, the patient in both instances being laid on the back, with a roll of clothing under the shoulders. In the Marshall Hall method the position is never supine, but is alternately prone and lateral. This is a very important practical difference, especially in drowning cases, for in such cases there is apt to be a considerable accumulation of watery mucus, and in the supine posture, with the head thrown back this will accumulate in the throat and obstruct the passage of air. An even greater disadvantage is the tendency of the limp and swollen tongue of the drowned subject to fall back and obstruct the air passage when in the supine posture. It is clear, therefore, that even if efficient in producing air exchange, both the Silvester method and the Howard method are contra-indicated in cases of drowning. The above objections do not apply to the Marshall Hall method; but on the other hand it is doubtful if the rolling of the patient on his side, which was looked upon by Marshall Hall as the essence of this method, adds greatly to its efficiency.

The most recent method which has been advocated for the resuscitation of the drowned was introduced in 1903 by Prof. E. A. Schäfer, and his work undoubtedly is one of the most



important contributions ever made to the literature of resuscitation. His technique was far more exact than that of previous investigators, and his experiments were made in a most thorough and scientific manner. He employed modern graphic methods, which, with few exceptions, had not been previously used. It is to this illustrious investigator that we owe an accurate knowledge of the large amount of water which may pass into and be absorbed by the lungs; the small amount of air expired in the act of drowning; the standard method of estimating efficiency by stating the amount of air exchanged, not with each movement of the chest, but in a given time—the five-minute standard; and a new process of artificial respiration—the Schäfer method. Further, he employed the living instead of the dead human body as the subject of many of his experiments. In studying the effects of drowning, dogs were used. The living human body was made use of to test the efficiency of the various methods of artificial respiration.

He found the amount of water sucked in during complete or partial submersion had no relation to the weight or size of the animal, and the amount was also found to vary greatly—varying from 75 cc. to 690 cc. Nor was there any relationship found between the possibility of recovery by artificial respiration and the amount of water taken in. If the animal was removed immediately after drowning, very little water was found in the lungs—it was found to be absorbed into the blood nearly as fast as it was taken in.

Schäfer observed that "the physiological phenomena of drowning are a form of the phenomena exhibited in all cases of asphyxia. They are modified, however, by the reflex effects of the contact of the water with the sentient surfaces of the skin, larynx and air passages; and these show themselves most markedly by a primary inhibition of respiration, which commonly occurs, as well as by an early and persistent tendency to cardiac inhibition. Contact of the water with the air-passages leads also to an increased secretion of mucus, and may offer an insuperable obstacle to the passage of air into or out of the alveoli and render futile any attempt at artificial respiration."

The tracings made by Schäfer show that the most common phenomena relating to the respiration are the following:

(1) An initial cessation (holding of the breath), which may last some 20 seconds.

(2) When resumed, the respirations are slow and may be irregular, but are deeper than normal and tend to increase in depth and slowness as asphyxia progresses. They are sometimes moderately slow and regular for a minute or two, and then become much slower; usually they cease somewhat abruptly.

(3) The total cessation of respiration takes place a variable time after immersion—sometimes in less than two minutes, sometimes not until five or six minutes, but usually in about three or four minutes; during these times water is being passed in and out of the air-passages.

With regard to the circulation, the most prominent features were found to be:

(1) A preliminary fall of arterial pressure, mainly due to cardiac inhibition, but vaso-dilatation was also a factor.

(2) An arrest of this fall, followed, in spite of greatly increased inhibition, sometimes by an actual rise of pressure, the arterioles constricting.

(3) A final fall of pressure, with increased slowing of the heart-beat. Sometimes this was accompanied by a gradual weakening of the beat; in these cases the blood-pressure fell steadily, coming down nearly to zero; the heart continuing to beat, with less and less force, for one or two minutes, in one case for as long as four and a half minutes, after cessation of respiration.

Schäfer found that the most effective method of resuscitating the animals after drowning was the compression of the thorax and abdomen either in the supine or in the prone position. In the former, occasionally he observed post mortem that the liver had been ruptured, with extravasation of blood into the abdominal cavity. In fact, this accident has been known to happen in the human subject after employment of artificial respiration in the supine posture.

There was great variability in the results of artificial respiration after drowning in the dog, even when the method employed was calculated to exchange a normal amount of air. As a general rule, if respiration had just ceased and the heart was still beating steadily, artificial respiration would restore life. But if the heart stopped simultaneously with the respiration or suddenly ceased soon after, the prospect of recovery was smaller.

Another point which was accentuated in these experiments was the limited time, after cessation of natural respiration, within which artificial respiration was likely to be effective. If more than two minutes was allowed to elapse after the natural respirations had ceased, failure to recover the animal was nearly always the result, even if the heart was still beating. The time, therefore, at one's disposal for the resuscitation of a drowned subject is measured out in small fractions of a minute; and it is no exaggeration to say that every second is of importance, and that no time should be employed in loosening clothing or in any preliminary operation, but that in all cases artificial respiration should be commenced without one instant's delay.

Schäfer and his assistants measured the gaseous exchange which occurred in the live human subject during artificial respiration by the methods of Silvester, Hall and Howard and found that by none of these methods could they produce as large an amount as by a new method which Schäfer suggested.

In this method, which he calls the "Prone Pressure Method of Artificial Respiration," the subject is allowed to lie prone, *i. e.*, face downwards. The operator kneels on one side of the subject, facing the head, and places his hands, close together, flat upon the back of the subject over the loins, the fingers extending over the lowest ribs. By now leaning forwards upon the hands, keeping the elbows extended, the weight of the operator's body is brought to bear upon the subject, and this not only compresses the lower part of the thorax but also the abdomen against the ground, the pressure being fairly equally

distributed. The result of this is that not only is the ~~thorax~~ diminished in extent from before back, but, owing to the pressure which is communicated to the abdomen, the viscera are compressed and tend to force the diaphragm up, so that the thorax is diminished in capacity from above down. This is no doubt the reason why the pressure method, when applied in the prone position, is more effective than when applied in the supine position as in Howard's method. The pressure is applied not violently, but gradually, during about three seconds, and is then released by the operator swinging his body back, but without removing his hands. The elasticity of the chest and abdomen causes these to resume their original dimensions, and air passes in through the trachea. After two seconds the process is again commenced, and is continued in the same way, the operator swinging his body forwards and backwards once very five seconds, or about 12 times a minute, without any violent effort and with the least possible exertion."

Experience has shown that a single person can employ this method without becoming fatigued or exhausted, which is not true of some of the other methods; and further, it is a very simple method and needs hardly to be taught. The reason why this method of Prof. Schäfer's is to be recommended in preference to any other method thus far described lies in its many obvious advantages, chief among these being the following:

- (1) Ease of carrying out the method.
- (2) Efficiency of gaseous exchange.
- (3) Extreme simplicity of the procedure.
- (4) Impossibility of the air-passages being blocked.
- (5) No risk to organs (liver, etc.).

Many objections have been registered against the method by such men as Bowles, Silvester and others; but up to the present time there is little doubt but that Prof. Schäfer's method is the simplest and most efficient one for the resuscitation of the apparently drowned. It has recently been adopted by the Royal Life Saving Society to the exclusion of any other, and undoubtedly this decision will result in the saving of many lives which would surely be sacrificed by the employment of the comparatively complex methods hitherto practised, since these require special training and in some cases considerable muscu-

lar power to carry out, and some, at least, are of doubtful efficacy.

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## THE GREAT IRISH CLINICIANS OF THE NINETEENTH CENTURY.\*

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When, a few days ago, I read a draft of the Home Rule Bill which the British government has introduced in Parliament, I wondered what the great medical worthies whose lives I have been studying would say if they were to reappear on the world's stage. They lived at a time when the tragic muse had not tears enough to bewail the fate of Ireland; at a time when the passions engendered by the Act of Union were still burning

fiercely; at a time when the two great Churches—each preaching the doctrine of love of fellow man—were hating and reviling each other in a manner that beggars description. When I read of some of the things that were done by the one to the other I could scarcely believe that I was reading of the nineteenth century; they imitated savages so faithfully!

I have an idea that of all the men whose story concerns us—Corrigan, Stokes, Graves and Cheyne—Graves alone would be actively interested in the great events in his country's history.

\* Read before the Medical History Club of Philadelphia, and in part before the A. M. P. O. Medical Fraternity.

He impresses me as the greatest of this quartet, a man wedded to his profession, yet with wide human interests. Graves all his life was in sympathy with the ancient philosopher who said, "Nihil humanum a me alienum puto." Stokes was a scholar, a good observer, with esthetic tastes, but not caring much for the great political questions that stirred his contemporaries. Occasionally he utters an altruistic platitude, but it is evident that his heart was not deeply moved. He was opposed to Home Rule, though he welcomed the Catholic Emancipation of 1829. As to Corrigan, it is difficult to ascertain how he stood in the critical days of Irish history. Belonging to what was at that time the unpopular faith in Ireland, though held by the majority, his official biographer of an opposite faith has done him scant justice. When I come to speak of his medical work, I shall have to break a lance in his behalf.

The fourth of the group was not an Irishman at all, but a Scotchman with the typical characteristics of that strong, yet sentimental race. His sympathies were evidently with the ruling powers, for he received high honors from them—no less a one than that of physician to His Majesty's forces in Ireland, a most distinguished post.

If they were to come to life, Graves and Corrigan would surely side with Redmond and Asquith, Stokes probably not. As for Cheyne, he, as we shall see, did everything with a motive. He was shrewd and calculating, and might have espoused Home Rule in Dublin and opposed it in Belfast. Perhaps I am doing his memory an injustice, but thus he has impressed me in his remarkable autobiography.

When we consider these men in their medical relations, one of the things that strikes us is the remarkable circumstance that the city of Dublin should have contained, at nearly the same time, four great luminaries. Yet it is not strange when we reflect that in the glorious days of Pericles there walked the streets of Athens men like Aeschylus, Thucydides, Phidias, Sophocles, Anaxagoras and Socrates. Graves and Stokes, and to a lesser degree Corrigan and Cheyne, made Dublin the third medical city in the world, Paris being first and Edinburgh second; and even Edinburgh at that time did not have a comparable galaxy. Dublin had not been heard of before, nor has it been heard of since. In our day few Americans go there, and they only for the vast experience obtainable in the great Rotunda Hospital; but in the first half of the nineteenth century it drew men from this and other countries who were eager to walk the wards of the Meath Hospital with Graves and Stokes, or the Harwicke Fever Hospital with Cheyne, or the small infirmary in Jervis Street presided over by Corrigan. By a curious coincidence, the volume of lectures by Graves which I consulted in my reading, and which I show you here, was purchased in Dublin by Moreton Stille, a graduate of the University of Pennsylvania and a brother of Alfred Stille, the famous professor of medicine in our university a generation ago. Moreton Stille went to Dublin for postgraduate study, and, though he did not remain there long, finding the opportunities offered by Vienna, where the great Skoda was at his zenith, more attractive, he acquired a high regard for both Graves and Stokes. These two were almost the only physicians

in the English-speaking world that were practising real bedside teaching. I cannot help thinking of Marion Sims, who was graduated in Philadelphia about the same time, or a few years earlier, without having ever seen a patient at close range. His graphic account of his experience when called to see a little child, his first patient, should be interesting to the students of our day who practically live in the wards of hospitals in their senior year.

It is difficult to say who deserves the greater credit, Graves or Stokes, for the introduction of bedside teaching. Graves was the older and probably the pioneer. Strictly speaking, Graves was not the first to do clinical teaching. Francis Bond preceded him in this country, and the great Boerhaave in Leyden. The first official attempt at clinical teaching, after the dissolution of the Aesculapian schools, had been made even earlier, in 1578, in the Hospital of St. Francis at Padua, by Albert Bottoni and Marc Oddo (Renouard, *Histoire de la Médecine*, Paris, 1846, p. 309). That practical bedside teaching, however, was in vogue more than eighteen hundred years ago appears from the following lines from Martial:

Languebam, sed tu comitas protinus ad me  
Venisti centum, Symmachus, discipulis.  
Centum me tetigere manus Aquilone gelatae,  
Nec habui febrem: Symmachus, nunc habeo.

I'm out of sorts, but Symmachus is here,  
His hundred pupils following in the rear;  
All feel my pulse with hands as cold as snow,  
I had no fever then—I have it now.

Graves' merit consists in having given the students opportunity to make routine observations of patients assigned to them, for reports of whose conditions they were held responsible. He was the first to break down "the impassable gulf which in that aristocratic era lay between the student and the teacher." His method in many respects is that in vogue in the best medical schools to-day.

#### GRAVES.

Robert James Graves (1796-1853) is the Trousseau of Ireland, a splendid observer, a brilliant lecturer, a fascinating writer. No man appreciated his qualities more than Trousseau himself, as may be seen in the following excerpt from a preface written by him to the French translation of Graves' lectures:

For many years I have spoken of Graves in my Clinical Lectures; I recommend the perusal of his work; I entreat those of my pupils who understand English to consider it as their breviary; I say and repeat that, of all the practical works published in our time, I am acquainted with none more useful, more intellectual; and I have always regretted that the Clinical Lectures of the great Dublin practitioner had not been translated into our language. . . .

As Clinical Professor in the Faculty of Medicine of Paris, I have incessantly read and re-read the work of Graves; I have become inspired with it in my teaching; I have endeavored to imitate it in the book I have myself published on the Clinique of the Hotel-Dieu; and even now, although I know almost by heart all that the Dublin Professor has written, I cannot refrain from perusing a book which never leaves my study. . . .

Although a clinical observer, he loves the accessory sciences; we see him frequently having recourse to physiology, in the domain of



which he loves to wander; to chemistry, with which he is acquainted, which he estimates at its true value, and to which he accords a legitimate place. . . .

Graves is, in my acceptance of the term, a perfect clinical teacher. An attentive observer, a profound philosopher, an ingenious artist, an able therapist, he commends to our admiration the art whose domain he enlarges, and the practice which he renders more useful and more fertile.

Graves' name is of course enshrined forever in the name Graves' disease, whether justly or not, I have not time to discuss. Nearly every country claims for some favorite son the honor of having first recognized the disease: England for Parry, Italy for Flajani, Germany for Basedow; and even in this country we have a possible claimant. Graves' original account is as follows:

I have lately seen three cases of violent and long-continued palpitation in females, in each of which the same peculiarity presented itself, viz., enlargement of the thyroid gland; the size of this gland, at all times considerably greater than natural, was subject to remarkable variations in every one of these patients. When the palpitations were violent, the gland used notably to swell and become distended, having all the appearance of being increased in size, in consequence of an interstitial and sudden effusion of fluid into its substance. The swelling immediately began to subside as the violence of the paroxysm of palpitation decreased, and during the intervals the size of the gland remained stationary. . . . The palpitations have in all lasted considerably more than a year, and with such violence as to be at times exceedingly distressing; and yet there seems no certain grounds for concluding that organic disease of the heart exists. In one, the beating of the heart could be heard during the paroxysm at some distance from the bed—a phenomenon I had never before witnessed, and which strongly excited my attention and curiosity. . . . The enlargement of the thyroid, of which I am now speaking, seems to be essentially different from goiter in not attaining a size at all equal to that observed in the latter disease. Indeed, this enlargement deserves rather the name of hypertrophy. . . .

A lady, aged twenty, became afflicted with some symptoms which were supposed to be hysterical. This occurred more than two years ago; her health previously had been good. After she had been in this nervous state about three months, it was observed that her pulse had become singularly rapid. This rapidity existed without any apparent cause, and was constant, the pulse being never under 120, and often much higher. She next complained of weakness on exertion, and began to look pale and thin. Thus she continued for a year, but during this time she manifestly lost ground on the whole, the rapidity of the heart's action having never ceased. It was now observed that the eyes assumed a singular appearance, for the eyeballs were apparently enlarged, so that when she slept, or tried to shut her eyes, the lids were incapable of closing. When the eyes were open, the white sclerotic could be seen to a breadth of several lines, all round the cornea. In a few months, the action of the heart continuing with unceasing violence, a tumor, of a horse-shoe shape, appeared on the front of the throat and exactly in the situation of the thyroid gland. This was at first soft, but soon attained a greater hardness, though still elastic. From the time it was first observed, it has increased little, if at all, in size, and is now about thrice the natural bulk of the fully developed gland of the female after the age of puberty. It is somewhat larger on the right side than on the left. A circumstance well worthy of notice has been observed in this young lady's case, and which may serve to throw light on the nature of this thyroid tumefaction. The circumstance I allude to is that from an early period of the disease a remarkable disproportion was found to exist between the beats of the radial and of the carotid arteries, those of the former being

comparatively feeble, while those of the latter were violent, causing a most evident throbbing of the neck, and accompanied by a loud rustling sound. In about fourteen months the heart presented all the signs of Laennec's passive aneurysm; the tumor in the neck is subject to remarkable variations in size, sometimes diminishing nearly one-half. None of her family have had goiters, nor was she ever in any of the usual localities of the disease.

In his Clinical Lectures Graves deals with general rather than with special subjects, while Stokes confines himself to diseases of the heart and lungs, and fever. Graves made a careful study of the epidemiology of cholera, and in a voluminous essay discusses the outbreak in England and elsewhere in the old world, and in the United States, taking his information about the latter from an article by a famous Professor of Medicine in the University of Pennsylvania, Samuel Jackson. Graves was the first to show clearly that cholera travelled, and travelled only along lines of human contact. "The results of this study of the epidemic led Graves to a suggestion, the importance of which to the well-being of the human race it would be hard to overestimate. Referring to our ignorance of the laws of epidemics, he proposed, with the view of determining these still hidden laws, that the different civilized governments of the world should unite in the wide establishment of medical observatories, in which, always in connection with a complete system of meteorological observation, careful records should be kept of the rise, progress, and character of disease, whether endemic or epidemic." It took the cholera 20 years to encompass the earth, while influenza, he remarks, "often traverses the same space in a few months."

Graves was a great traveller and a remarkable linguist. On one occasion when on a pedestrian journey in Austria, having neglected to carry his passport, he was arrested as a spy and thrown into a dungeon. His assertion that he was a British subject was disbelieved by the authorities, who insisted that no Englishman could speak German as he did. In his imprisonment, which lasted ten days, he suffered great privations.

Unlike Stokes, he had a keen sense of humor, as the following extract from one of his letters reveals. While in Rome he found sleeping difficult, due to the presence in all bed-rooms "of a certain animal which, together with the culices and ranae palustres, may have robbed Horace of a night's rest on the journey to Brundisium. A friend of mine was so tormented by their bites that when visiting the capitol he flung, in a fit of rage, thirty of the ringleaders headlong down the Tarpeian rock."

Toward his patients he was exceedingly kind. He denounced the practice prevailing in France and in Ireland of discussing hopeless cases in the presence of the patients. I find that our present method of bedside teaching is at times conducive to the same reprehensible practice that so outraged Graves' sense of propriety. Students, when asked to give their opinion of the nature of a case, often use terms understood by the laity—cancer, tuberculosis, Bright's disease—forgetting what a terrible effect such a word may have on the mind of the patient. These terms should never be employed within the hearing of the sick.

Graves' achievements in medicine apart from his discovery

of exophthalmic goiter are many, but none gives him greater claim to immortality than the part he took in revolutionizing the treatment of fevers. Up to his time fever patients were starved. Graves insisted that such patients must not be allowed to suffer from starvation. He says:

In a patient laboring under fever and a protracted abstinence, whose sensibilities are blunted and whose functions are deranged, it is not at all improbable that such a person will not call for food, although requiring it; and if you do not press it on him, and give it as a medicine, symptoms like those which arise from starvation in the healthy subject may supervene. . . . You may, perhaps, think it unnecessary to give food, as the patient appears to have no appetite, and does not call for it. You might as well think of allowing urine to accumulate in the bladder because the patient feels no desire to pass it. You are called upon to interfere where the sensibility is impaired, and you are not to permit your patient to encounter the terrible consequences of starvation because he does not ask for nutriment.

Stokes, in his sympathetic biography, quotes the following story:

Graves was going round the hospital, when, on entering the convalescent ward, he began to expatiate on the healthy appearance of some who had recovered from severe typhus. "This is all the effect of our good feeding," he exclaimed; "and lest, when I am gone, you may be at a loss for an epitaph for me, let me give you one, in three words: 'He fed fevers.'"

Graves was largely responsible for the opium treatment of peritonitis, which proved so valuable and was extensively employed up to the period when peritonitis ceased to be a medical disease and became a surgical affection.

His ideas on the subject of tuberculosis were far in advance of his time and are practically those universally adopted to-day. He writes thus (Clinical Lectures, New Sydenham Society, Vol. 2, p. 118):

Make your patient lay aside slops and tea and let him take whole-some fresh meat, bread and good beer. He should rise early and breakfast early, let him dine, also, early. When the weather permits, let him remain in the open air four or five hours, taking exercise on a jaunting car or on the top of a coach. Never abandon cases of consumption.

The best climate for the treatment of consumption, in his opinion, is that of the East and West Indies, South Carolina, Florida, the northern states of South America or Egypt.

As I have said before, Graves was deeply interested in the political events of his time, especially in the Hungarian Revolution and in Great Britain's Asiatic policy, which he studied with the zeal of a responsible diplomat. He was interested in art and did some painting. On a journey in Italy he formed a friendship with the artist Turner that had a great influence upon his life. A curious anecdote is told of their first meeting. They travelled together for months, enjoying each other's company, sketching side by side, without either inquiring the name of his comrade, and it was not until they reached Rome that Graves learned that his companion was the great artist.

#### STOKES.

William Stokes (1804-1878) came of a long line of distinguished men. He was an indolent youth, fonder of reading

\* These words are, however, not on his tombstone.

poetry and romance, especially the tales and ballads of Sir Walter Scott, than of Latin and mathematics. His son tells how he was roused from his lethargy:

One day, while in his favorite retreat, he fell asleep but shortly afterwards was awakened by some warm drops falling on his face. He started up and saw his mother bending over him. Her tears had awakened him. Stung with remorse at having been the cause of so much suffering, his nature appeared to undergo a complete and salutary change, and the dreamy, indolent boy suddenly became the ardent, enthusiastic student.

He had no college training, but was educated by his father and private tutors. After taking courses in chemistry in Glasgow he matriculated in the Edinburgh Medical School, where he fell under the spell of Dr. Alison. Alison must have had a marvelous personality, judging by what Stokes and another pupil, Acland, say about him. While yet a student, Stokes wrote a small volume on the use of the new and much ridiculed instrument called the stethoscope,\* and to him is due much of the credit for popularizing Laennec's great invention. Returning to Dublin, he was at once elected physician of the great Meath Hospital in the place of his father, who had resigned. Here he became the colleague of Robert James Graves, with whom he worked side by side in friendly relationship for nearly thirty years. In 1842 he was chosen Regius Professor of Physic in succession to his father, who had held the same chair. At the height of his career, Graves having died, he was probably the ablest physician in Europe. Diseases of the heart and lungs especially interested him, and there are few chapters in these subjects that he has not enriched. He understood better than his contemporaries, better even than the school of Laennec and than many of his successors, that the murmur is not everything either in the diagnosis or in the prognosis of diseases of the heart, and that a functional diagnosis is of more importance than an anatomic one. It is comforting to the student and the practitioner to read of the modesty of a man who had studied heart murmurs better than probably any man since his day—barring perhaps the elder Austin Flint. In one place he says:

We read that a murmur with the first sound, under certain circumstances, indicates lesion of the mitral valves. And again, that a murmur with the second sound has this or that value. All this may be very true, but is it always easy to determine which of the sounds is the first, and which the second. Every candid observer must answer this question in the negative. In certain cases of weakened hearts acting rapidly and irregularly, it is often scarcely possible to determine this point. Again, even where the pulsations of the heart are not much increased in rapidity, it sometimes, when a loud murmur exists, becomes difficult to say with which sound the murmur is associated. The murmur may mask not only the sound with which it is properly synchronous, but also that with which it has no connection, so that in some cases even of regularly acting hearts, with a distinct systolic impulse, and the back stroke with the second sound, nothing is to be heard but one loud murmur. . . .

So great is the difficulty in some cases, that we cannot resist altering our opinions from day to day as to which is the first and which the second sound.

\* The attitude of the medical profession toward the stethoscope in the early days of its use is well illustrated in Oliver Wendell Holmes' poem, "The Stethoscope."

Stokes was one of the first to urge a definite required course of gymnastics or pedestrian exercise in the treatment of heart disease. His ideas on tuberculosis were remarkable, considering how inadequately he knew the pathology of the disease. He believed in the curability of phthisis even after excavation has formed. (Diseases of the Chest, p. 474.) His treatment in its essentials differed but little from that in vogue to-day. The patient was first put to bed and then was allowed to be about, taking exercise in mild weather and afterwards removing to a milder climate to perfect his recovery.

In a case with cavity (Diseases of the Chest, p. 474), yet in which the symptoms and signs are not progressive, the patient's best chance I believe to be the use of a seton, and travelling. If he does not recover, his life will be probably prolonged. He should take as little medicine as possible; he should adopt all strengthening means, and use such a regimen as experience points out as the best. Heated rooms, cough mixtures, acid draughts, inhalations, narcotics, repeated counter-irritation, and all the varied and harassing treatment which ignorance supposes to be curative, these are not the means of recovery.

The association of his name with the peculiar type of breathing called Cheyne-Stokes breathing, and with a strange malady of the heart—slow pulse and cerebral symptoms—Adams-Stokes disease, will assure him an easy immortality. The respiratory symptom was first observed by Cheyne (Dublin Hospital Reports, Vol. 2, p. 217) in a case of fatty degeneration of the heart. I shall refer to this later on. The Adams-Stokes syndrome was first noticed by Robert Adams, a surgeon, in 1827, but Stokes's careful analysis of Adams's case, as well as his own observations, makes him virtually the real discoverer. The condition is characterized by repeated attacks of syncope, pseudoapoplexy, convulsions, and permanently slow or irregular and feeble pulse.

The original account of Adams' disease appeared in a paper on "Cases of Diseases of the Heart Accompanied with Pathological Observations," in the Dublin Hospital Reports, 1827, IV, 353, and is as follows:

An officer in the revenue, aged 68 years, of a full habit of body, had for a long time been incapable of any exertion, as he was subject to oppression of his breathing and continued coughing. In May, 1819, in conjunction with his ordinary medical attendant, Mr. Duggan, I saw this gentleman; he was just then recovering from the effects of an apoplectic attack, which had suddenly seized him three days before. He was well enough to be about his house, and even to go out. But he was oppressed by stupor, having a constant disposition to sleep, and still a very troublesome cough. What most attracted my attention was, the irregularity of his breathing, and remarkable slowness of the pulse, which generally ranged at the rate of 30 a minute. Mr. Duggan informed me that he had been in almost continual attendance on this gentleman for the last seven years; and that during that period he had seen him, he is quite certain, in not less than 20 apoplectic attacks. Before each of them he was observed, for a day or two, heavy and lethargic, with loss of memory. He would then fall down in a state of complete insensibility, and was on several occasions hurt by the fall. When they attacked him, his pulse would become even slower than usual, his breathing loudly stertorous. He was bled without loss of time, and the most active purgative medicines were exhibited. As a preventive measure, a large issue was inserted in the neck, and a spare regimen was directed for him. He recovered from these

attacks without any paralysis. Œdema of the feet and ankles came on early in December; his cough became more urgent, and his breathing more oppressed; his faculties, too, became weaker.

In one respect Stokes, so advanced a student of cardiac and pulmonary diseases, was reactionary and hopelessly conservative, namely in his attitude toward fever. A word that we now use in the sense of a symptom, he and his contemporaries employed as the name of a disease. And so we read of fever, its symptoms and treatment, as we read to-day of pneumonia. At first this is somewhat confusing, but the matter becomes clear when we realize that the fevers known in Ireland were chiefly typhus and intermittent malaria. The Irish typhus stood a close second to emigration in decimating the population of Ireland; for many years it had epidemic exacerbations, as for instance in 1847-48, about the time of the great famine, during which it caused frightful devastation, even among physicians. Stokes, good pathologist that he was in regard to diseases of the heart, believed in the essentiality of fever and looked upon anatomic lesions as accidental and unimportant complications. This view naturally caused him to consider typhus fever and typhoid fever, which also occurred in Dublin, one and the same disease, an opinion which he maintained until his death in 1878. When one remembers that in 1837 Gerhard and Pennock, in Philadelphia, clearly showed that typhus fever without intestinal lesions and typhoid fever with intestinal lesions, the *fièvre typhoïde* or *dolhiéentérite* of the French, were totally distinct diseases, and that Lombard of Geneva a year earlier had made the same claim, one realizes how averse Stokes was to changing his opinion. This was no doubt due to his conservative character. As he himself says, "There is nothing more difficult than for a man who has been educated in a particular doctrine to free himself from it—even though he has found it to be wrong." Even intermittent fever was to Stokes merely a variety of fever, a typhus variant, and not a distinct entity. Certainly this tenacity of view is remarkable, as his death occurred only two years before Laveran's discovery of the *Plasmodium malariae*.

Stokes's ideals of medical ethics were of the highest. The following are some of the principles laid down by him. They need neither explanation nor emphasis:

Never, when brought in as a consultant, declare the nature of a disease in the absence of the medical attendant.

Never hold that you have any property in a patient; be tolerant with the sick in their restless desire to seek other advice; preserve your independence; eschew servility.

As regards conduct in society, never allude to your success in practice. Be silent when quackery is discussed. Be tolerant when those who converse on medicine, while ignorant of its foundation, reject legitimate medicine.

Never originate discussion on medical topics in conversation. As regards conduct toward the profession, consider first the patient, second your professional brother, lastly yourself. Be reticent, lest by a casual word upon the previous treatment of the case, you inflict a stab in the dark on your brother's reputation.

When patients come from the country, never ignore their local attendant, only correspond with them through him.

Do not communicate any fresh discovery in the case that you may make, without communicating such first to him.



Make no change of treatment without writing your opinion to him. Have no professional quarrel.

Like a wise physician, Stokes had his non-medical hobbies. He was fond of music, a student of Shakespeare, a lover of art and an art critic, and an archeologist of no mean ability. By reason of these cultural interests his home was the meeting-place of the intellectuals of Dublin and in it all the distinguished visitors to the city were entertained. On one occasion Carlisle spent an evening at Stokes's house. Perhaps because of his unconquerable Hibernophobia, Carlisle was anything but pleased with his visit, while Stokes pronounced Carlisle not only a bore, but a hyperborean.

The writings of Stokes are voluminous, but of them all the work on the Heart and Aorta and those on Diseases of the Chest are, and will remain, medical classics. His fame would be greater if he had not written his monograph on Fever. Many were the honors conferred upon him. The one he prized the most was the *Ordre pour le Mérite*, bestowed upon him by the German Emperor in 1876. His biographers say he was elected a member of the National Institute of Philadelphia. I have searched in vain for this institute. The name cannot refer to the American Philosophical Society or the Academy of Natural Sciences, of neither of which was Stokes a member.

#### CORRIGAN.

Sir Dominick Corrigan (1802-1880) is known to all of us through the Corrigan pulse. His article on permanent patency of the aortic valves, in the *Edinburgh Medical and Surgical Journal* for 1832, written only seven years after his graduation, is a masterpiece and a classic. Although historians say that he was not the first to describe the condition, Vieussens and Hodgson having preceded him, there is no doubt that his description is the best even to this day, and that justice is not outraged by preserving his name in connection with the disease. It is a remarkable fact that Corrigan studied the condition clinically and pathologically in an institution where he had but six beds. As Walsh says ("The Irish School of Médecine," *Johns Hopkins Hospital Bulletin*, September, 1906):

He did not visit his hospital merely to see patients, but to study the cases carefully. His success is only another example of the necessity for seeing much, and not many things, if there is to be any real progress. In our day, physicians scarcely consider that they have any hospital experience unless they are attending physicians to several hospitals, seeing at least one hundred patients a week. The result is that patients do not receive the skilled care they should, and that advance in medicine suffers because of the wasted opportunities for clinical observation while a busy attending physician rushes through a ward and the resident physician has only time for the routine work that enables him to keep just sufficiently in touch with the progress of his cases to satisfy the hurrying chief physician.

Corrigan's writings are few. Aside from articles in journals, all I have found is a small monograph on Fever published in Dublin in 1853. Like his contemporaries, he believed in the primary nature of fever and looked upon anatomic lesions as secondary results and not as essential parts of the process; but unlike Stokes and Graves, he differentiated much more clearly

ordinary typhus from what he called insidious typhus or follicular enteritis, which is our typhoid. I am inclined to think Corrigan was not well-read in the literature of his time, for he seems to have had an open mind which would have been quickly guided aright by a study of the works of others, especially those of Gerhard and Pennock. To that extent I agree with his biographer, Norman Moore, although I think the latter is too severe in his general judgment that Corrigan is a much overrated man. The monograph on Fever shows clear insight and sound judgment, and his attention to details in treatment is admirable. In some conditions his practice was truly heroic, as when he advised blistering the entire abdomen for tympanites. Like the great George B. Wood, he was a believer in turpentine, which he gave in large doses for the same condition. A few years ago the medical profession was startled by the announcement that quinine in large doses was a cure for pneumonia. A number of articles have been written on this supposedly new discovery, yet Corrigan in 1856 (*Dublin Hospital Gazette*, 1856, III, 177) advocated the same treatment.

#### CHEYNE

I have chosen to include John Cheyne (1777-1836) in the list of the great Irish clinicians. As a writer he has no claim to be placed on a par with the others. But as a great practitioner, a good observer, and a generally remarkable man, his life is worthy of a little study. I have said he was a Scotchman, the son of a Leith physician whom he began to assist in leeching and bandaging at the tender age of 13. He was sent to the medical school in Edinburgh at 16, too young, he himself confesses, and was graduated at 18 by the aid of a "grinder." Under the inspiration of Sir Charles Bell he became absorbed in pathologic studies and in diseases of children. But he did not find Edinburgh a congenial field for practice. On looking about for a new location, he observed that in Dublin the medical profession was highly respected, and so he settled there. His method of study was one that on many occasions I have admired my own students to follow. When he observed a well-marked case of a disease, or when an epidemic broke out, he studied the best monograph obtainable on the subject.

Cheyne early in his career endeavored to become acquainted with the characters of those who moved in the highest ranks in the profession, hoping by discovering the cause of their success to follow in their footsteps. Nevertheless, practice in Dublin was slow in coming to him. The few friends he had advised him to go into company and to give entertainments to those who had it in their power to advance his interests. At last he yielded—reluctantly he says—but finding that his own circumstances did not permit of return entertainments for others, he refused to repeat the experiment. After his election to the Meath Hospital and to a lectureship in the College of Physicians, his practice grew by leaps and bounds. In 1816, six years after coming to Dublin, it amounted to £17.10 or about \$8600, and soon reached an average of £5000 or \$25,000, which it maintained for ten years. Being of a weak constitution, he was obliged to circumscribe his practice by refusing to go a distance from Dublin or to undertake attendance upon patients

in the country. He was sure that had his health permitted he could have added £1500 to his income, making it \$32,500 a year. Considering the purchasing power of money in the year 1820, Cheyne must have had a practice that is equalled by few living physicians in the United States.

Many of his statements, in their frankness and their shrewdness, remind one of Benjamin Franklin's autobiography. I cannot do better than to quote a few characteristic paragraphs which very clearly show Cheyne's diplomacy, as well as insight into human nature.

As I was much more generally employed as a consulting than as an attending physician, I endeavored to escape interruption in my chief line of business. I returned to my home at appointed times to form new engagements, but I left no account of my route when I set out from home. When I was tracked and obliged to yield to an unexpected requisition, the patient for whom I was sent was perhaps dead; or he was dying and I was unable to leave him; or the attack was over and he was again well, and my sole recompense was a complimentary speech; or I was led to supersede the family physician engaged elsewhere, which gave rise to explanations, and to a negotiation to replace him in attendance. In the meantime, disappointment to those patients and their medical friends who were waiting for me necessarily occurred, and thus a ruffle of the spirits, very unfavorable to the consideration of a difficult case, arose and continued for hours.

He always observed punctuality, which was not practised in Ireland, yet nowhere regarded with more complacency.

When a case of disease was assuming an unfavorable aspect, and when the question was mooted, "To whom shall we apply for further help?" it has, in a multitude of instances, been decided in my favor solely by the consideration that I would appoint the earliest hour for the meeting, and that I might be expected to appear within five minutes of the appointed time. . . .

I always endeavored to prevent changes of the medical attendants in a family unless in cases of obvious neglect or ignorance; and even then I never hinted at a substitute. If requested by a patient to recommend a surgeon, accoucheur, or apothecary, to attend in his family, I mentioned the names of three or four men of established character, and advised my patient to discuss their merits with his friends, and decide at his leisure. . . .

I was much employed in the families of my brethren. I found this a painful distinction. . . .

It must, however, be admitted that professional success, like every other good thing in this life, has in its nature many seeds of decay. The same circumstances which tended to bring the present favorite into general repute are probably already operating in

behalf of his destined successor. Thus, the physician to whom his fellow-citizens award the possession of the most skill is generally called upon to assist when all assistance is too late, and sarcastic remarks tending to promote his downfall are made when the patient dies and becomes the subject of ephemeral talk.

Cheyne's writings are few. The most important, aside from his autobiography, is the article to which I have already referred, in which he described the arhythmic breathing known as Cheyne-Stokes respiration. The following are his words:

For several days (the patient's) breathing was irregular; it would entirely cease for a quarter of a minute; then it would become perceptible, though very low; then by degrees it became heaving and quick; and then it would gradually cease again. This revolution in the state of his breathing occupied about a minute, during which there were about 30 acts of respiration. ("A Case of Apoplexy in which the Flethy Part of the Heart was Converted into Fat," Dublin Hospital Reports, 1818, II, 216.)

At the end of his forty-ninth year he became affected with a species of nervous fever. He continued working until 1821, when failing health compelled him to give up work, at a time when his income had reached phenomenal proportions. He retired to Sherrington, a country village of England, devoting himself to a modicum of practice and a large amount of religious contemplation. He does not state the nature of his disease; but as he had a cataract and gangrene in the lower extremities, it is fair to infer that he had diabetes, possibly also arteriosclerosis.

I am at the end of my essay. The four men of whose lives I have told you something all had remarkable personalities, which would win renown for them if they were living to-day. Without the advantages of the microscope, the thermometer, the blood-counting apparatus, and the numberless devices that aid us in the diagnosis and treatment of disease, they accomplished a great deal, enough to make them immortal, by the aid of their sense of touch and of hearing. Are we not making a mistake in our day by relying too much on instruments of precision? Can we not take a lesson from these men and train our powers of observation as they did? There are many undiscovered clinical facts—perhaps diseases—which another Graves and another Stokes, coming after us, will see. Then his contemporaries will wonder why we of the twentieth century were so blind.

## A REVIEW OF THE LIFE OF SIR HANS SLOANE, BART., M.D.\*

By JOSEPH T. SMITH, M.D.

"We are much beholden," says Bacon, "to Machiavelli and others that wrote what men do and not what they ought to do"; we are beholden to those who have written about Sir Hans Sloane, for his life was full as well as rich in those activities which are for the uplift of humanity. He has left deep and lasting footprints on the sands of time.

His father, Alexander Sloane, settled in Ireland at the head

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of a Scotch colony sent out by James I and was made receiver-general of taxes. His mother, Sarah, was the daughter of the Rev. Dr. Hicks, chaplain to Archbishop Laud. Hans, the seventh son, was born in Killyleah, County Down, Ireland, April 16, 1660.

Hans was so delicate in his early life that he had to forego the sports and pastimes indulged in by the boys of his age. When he was 16 he had an attack of hemoptysis and for three years was in very poor health. At that time he gave up the use

of wines and beer and lived a temperate life. Jardine says he took as his maxim "That sobriety, temperance and moderation are the best preservatives that nature has vouchsafed to mankind," and he adhered to those principles throughout a long life. Edwards says that his sickness served to strengthen the prudential elements in his character. It is not often that we find men turning their sicknesses to account and learning from them how to live.

He came to London at the age of 18. Staphorst was his teacher in chemistry, and he studied botany under Magnol and Tournefort. It was while at the "Jardin des Plantes" that he had Tournefort as his companion; in this garden he found a much wider field than any that could be availed of in England and, full of interest and enthusiasm over the new treasures spread out before him, he made the best use of his opportunities.

He studied medicine in Paris, where he had the advantage of having Du Verney as his anatomical instructor, and in Montpellier. In 1683 he received the degree of doctor of medicine from the University of Orange, and in 1701 the same degree from Oxford. After his graduation he came to London and took up his residence with Sydenham. This noted physician gave him the most active support and exerted his influence in introducing him into practice.

Two years after his graduation, in 1685, he was elected a member of the Royal Society, and four years after, in 1687, a Fellow of the College of Physicians. It is remarkable that one so young should have been elected to membership in these societies, and it was doubtless due to his preliminary training under men who, being in the advance guard of progress, stimulated his natural abilities in the right way.

In 1687, four years after graduation, and with the brightest outlook for a large and influential practice, he left London and joined the suite of the Duke of Albemarle on a trip to Jamaica, under the following conditions: "If it be thought fit that Dr. Sloane go as physician to the West Indian Fleet, the surgeons of all ships must be ordered to observe his directions. . . . He proposes that six hundred pounds, per annum, be paid to him quarterly, with a previous payment of three hundred pounds, in order to his preparation for this service. . . ." He was on the island fifteen months and in that short time gathered 800 new species of plants. This collection he gave to John Ray, who, in writing his noted work, the History of Plants, used very extensively the material he had received from Dr. Sloane. During his visit, the rich and the poor called upon him for medical advice; this he always gave freely and heartily, treating all who called him with equal consideration and taking nothing from the poor. On one occasion he was taken sick, and he says: "I had a great fever, though those about me called it a little seasoning." Writing about an earthquake, he says: "Ever since the beginning of February I dread earthquakes more than heat. For then we had a very great one. Finding the house to dance and the cabinets to reel, I looked out of the window to see whether people removed the house (a wooden structure) or no. Casting my eyes towards an aviary, I saw the birds in as great concern as myself. Then another terrible shake coming, I apprehended what it was and betook

me to my heels to get clear of the house; but before I got down stairs it was over."

In addition to Jamaica he visited Madeira, Barbadoes, Nieves and St. Christopher. He invested largely in Peruvian bark, as that was a very lucrative article of commerce, and made good use of it financially and medically. He has this to say of a dolphin which was caught and cooked: "Dry, though pretty good victuals, and well tasted; the nearer the head the more it is prized, although I am apt to think that if this fish, so much commended by sailors, was ashore in a market where other fish were to be had, it would not be counted so great a delicacy." He says in regard to his entertainment by the Governor of Barbadoes: "For my own part, I liked so well the dessert after dinner, which consisted of shaddocks, guavas, pines, mangrove, grapes, and other unknown fruits in Europe, that I thought all my fatigues well bestowed when I came to have such a pleasant prospect."

In 1696 he published an elaborate catalogue in Latin of the plants he had collected in Jamaica, which gave rise to much criticism, Leonard Plukenet, a learned botanist, attacking it. In 1707 he published the first volume of his book entitled "A Voyage to the Islands Madeira, Barbadoes, Nieves, St. Christopher and Jamaica, with the Natural History of the Herbs, and Trees, four-footed Beasts, Fishes, Birds, Insects, Reptiles &c. of the last of those Islands: to which is prefixed An Introduction wherein is an account of the Inhabitants, Air, Waters, Diseases, Trades &c. of that place, with some Relations concerning the Neighboring Continent, and Islands of America." . . . "Many shall run to and fro, and knowledge shall increase." Dan. xii: 4. The second volume did not appear until 1724, for the reason, as the author states, that "A multiplicity of business in the practice of physic, which I esteem one of my first cares and must be minded if the lives of persons be regarded with due attention to the several symptoms and changes of their diseases." Dr. Pulteney says: "They exhibit proof of the author's veracity, which I conceive it is difficult to parallel in any other work." The account of the Irish potatoes is interesting. Dr. Sloane says: "Many live on the Irish potatas, a sort of Solanum, on which, I have heard, they live in the mines of Potosi and in Ireland. . . . The root is tuberous; for shape and bigness very uncertain; but being for the most part oblong; as big as a hen's egg from a swelled middle tapering to both extremes; yellow and sweet within; when roasted, tasting like a boiled chestnut, and having many fibrils by which it draws its nourishment. . . . In four months after planting they are ready to be gathered, the ground being filled with them, and if they continue therein any longer, they are eaten by worms." He brought home a live snake and says: "Thus it lived for some time, when, being weary of its confinement, it shoved asunder the two boards on the mouth of the jar, and got up to the top of a large house, wherein lay footmen and other domestics of her grace the Duchess of Albemarle, who being afraid to lie down in such company, shot my snake dead." Dr. Pulteney says: "The voyage of Dr. Sloane was productive of much benefit to science by exciting an emulation both in Britain and on the Continent. . . . Several circumstances concurred, re-



specting the voyage of Dr. Sloane to Jamaica, which rendered it peculiarly successful to Natural History. He was the first man of learning whom the love of science alone had led from England to that distant part of the globe . . . "

In 1693 he was made secretary of the Royal Society and editor of the Philosophical Transactions. The editorship he held for twenty years. Edwards says: "The Philosophical Transactions of the Royal Society owe a great deal to Sloane; upon the death of the editor, Oldenburg, a diminution of the income of the Society and some personal disagreements in the Council Board impeded their publication, but Sloane bestirred himself and steadily and persistently built up the Transactions. He frequently gave prominence to medical subjects in the Transactions, so much so as to arouse complaint. . . . If Sloane, in his day, occasionally made scientific men somewhat more familiar with medical subjects than they cared to be, he did very much to make medical men aware of the peculiar duty under which their profession laid them of becoming also men of true science. It was one of the minor, but memorable results of the establishment of the Royal Society that it tended powerfully to lift medical practice out of the slough of quackery."

In 1700 Sloane was made the subject of a satirical pamphlet which appeared under the title "Transactioneer with some of his Philosophical Fancies." Trivial in itself, it nevertheless led to discussions which left their marks upon the Society for a long time. Sloane thought a member of the council, a Dr. Woodward, the author; this the doctor denied, but indorsed the satire. The ill-feeling lasted a long time. "The petty discussion came to a height when Sloane chanced to make some passing medical comment on the words the 'bezoar of gall-stone' . . . Sloane's casual remark drew from Woodward the offensive words, 'No man who understands anatomy would make such an assertion.'" Again he interrupted Sloane by exclaiming: "Speak sense or English and we shall understand you." Friends tried to enlist the president on Woodward's side by reminding him that he had often been patient under the medical dissertations, but Newton replied: "For a seat in the council a man should be a moral philosopher as well as a natural one." Woodward was removed as a member of the council, but Dr. Sloane sought a speedy reconciliation.

In 1686 Dr. Sloane was opposed to Halley for assistant secretary of the Royal Society. On the first ballot there was no election, and Sloane lost on the second. Sir Hans thus had his troubles in that great Society. In 1727 he succeeded Sir Isaac Newton as president of the Royal Society, retiring from it at the age of 80.

In 1694 he was made physician to Christ's Hospital; he gave all his salary to its foundation and retired after thirty years' service. .

In 1705 he was elected censor of the College of Physicians and was re-elected in 1709-1715. In 1719 he was elected president of the College of Physicians, and he remained in office 16 years. In the College of Physicians he warmly promoted the plan of a dispensary for the sick poor; this met with much opposition from the apothecaries. He advanced £700 to the college and later gave it £100.

In 1708 he was elected a foreign member of the French Academy of Sciences and shortly afterwards a member of the Imperial Academy of St. Petersburg and of the Royal Academy of Madrid.

In 1729 a very unique and interesting Epistolary Letter was published from T—— H—— (Thomas Hearne) to H——s S——e (Hans Sloane). Two hundred copies were published, two of which are in the Congressional Library at Washington, numbered 22-23, Second Edition. It is as follows:

*Since you Dear Doctor, saved my life  
To bless by Turns and plague my wife.  
In Conscience I'm obliged to do  
Whatever is injur'd by you;  
According then to your Command;  
That I should search the Western Land  
For curious things of every kind,  
And send you all that I could find:  
I've ravaged Air, Earth, Seas and Caverns,  
Men, Women, Children, Towns and Taverns;  
And greater Rarities can show  
Than Gresham's Children ever knew;  
Which Carrier Dick shall bring you down  
Next time his Waggon comes to town.  
I've got three drops of that same shower  
Which Jove in Danae's Lap did pour.  
From Carthage brought: The Sword I'll send  
Which brought Queen Dido to her end.  
The Stone whereby Goliath dy'd  
Which cures the Head-Ache well applied.  
The Snake Skin which you may believe  
The Devil cast who Tempted Eve.  
A Fig-leaf Apron, 'tis the same  
Which Adam wore to hide his Shame;  
But now wants Darning. I've beside  
The Blow by which poor Abell D'y'd.  
A Wet Stone were exceeding small,  
Time us'd to whet his Scythe withall.  
The Pidgeon Stuft, which Noah sent  
To Tell him where the Waters went.  
A Ring I've got of Sampson's Hair  
The same which Dalilah did wear.  
St. Dunstan's Tongue, which Story shows  
Did pinch the Devil by the Nose.  
The very Shaft as all may see  
Which Cupid shot at Anthony.  
And what above the rest I prize.  
A Glance of Cleopatra's Eyes.  
Some Strains of Eloquence, which hung  
In Roman Times on Tully's Tongue.  
Which long conceal'd and lost had lain  
Till Couper found them out again.  
A Goad if rightly us'd, will prove  
A certain Remedy for Love.  
As Moore cures Worms in Stomach bred.  
I've Pills cures Maggots in the Head,  
With the Receipt too, how to make 'em.  
To you I'll leave the Time to take 'em.  
I've got a Ray of Phaebus Shine  
Found in the bottom of a Mine.  
A Lawyer's Conscience, large and fair,  
Fit for a Judge himself to wear.  
In a Thumb Vial you shall see  
Close Cork'd some Drops of Honesty;  
Which after searching Kingdoms round,  
At last were in a Cottage found.*

*An Antidote, if such there be,  
Against the Charm of Flatery.  
I har't collected any Care,  
Of that there's plenty every where.  
But after wondrous Labor spent,  
I've got one Grain of rich Content.  
It is my Wish, it is my Glory,  
To furnish your Nicknackatory.  
I only beg when'er you show 'em  
You'll tell your friends to whom you owe 'em  
Which may your other Patients Teach  
To do as has done*

Yours

T. H.

In 1745 he issued his only medical publication, entitled: "An Account of a most efficacious Medicine for Soreness, Weakness, and Several other Distempers of the Eyes." A few extracts may be of interest. After writing of the difficulties he experienced in securing the receipt, he says:

Take of prepared Tutty, one ounce; of Lapis Hæmatitis prepared, two scruples, of the best Aloes prepared, twelve grains, of prepared Pearl, four Grains. Put them into a Porphyry, or Marble Mortar, and rub them with a Pestle of the same stone, very carefully, with a sufficient Quantity of Viper's Grease, or Fat, to make a Liniment, to be used daily, Morning and Evening or both, according to the Convenience of the Patient; as hereafter directed. . . . The Method which has succeeded with me in facilitating the efficacious Use, of the Liniment, is to bleed and blister in the Neck and behind the Ears, in order to draw off the Humors from the Eyes; and afterwards, according to the Degree of the Inflammation, or Acrimony of the Juices, to make a Drain by issues between the Shoulders, or a perpetual Blister. And for washing the Eyes, I generally recommend Spring Water, which I think preferable to any Spirituous Lotion, whether simple or compound. And the best inward Medicine I have experienced to be Conserve of Rosemary Flowers; Antiepileptic Powders, such as Pulvis ad Guttetam; Betony, Sage, Rosemary, Eyebright, wild Valerian Root, Castor etc. washed down with Tea made of some of the same Ingredients: as also Drops of Spirit, Lavendulæ composit, and Sal volat oleos. If the Inflammation return, drawing about six Ounces of Blood from the Temple by Leeches or Cupping on the Shoulders, is very proper. The Liniment is to be applied with a small Hair Pencil the eye winking or a little opened. . . .

He says Dr. William Stokeham told him, "He had learnt the great Virtue of Viper's Grease or Fat, in the cure of Diseases of the Eyes . . ."

And this, indeed, I judged so very reasonable, that I substituted that Grease, or Fat, in the Place of Hog's Lard which was in the original Receipt; and found, that it added so much to the efficacy of the Medicine, as to make it do, what I thought, wonders. . . . I communicated it to the late Dr. Arbuthnot: who after repeated Trials of that fat alone on sore eyes, has so high an Opinion of its Virtues, that he looked on it as equally beneficial with the whole Medicine. It is an Observation made by many Naturalists, that those Serpents cast their Skins every year, and with them the coverings of their Eyes; but how far, or whether at all, their fat is concerned in this Phenomenon I leave others to determine. . . .

In writing of the ill effects of Olive Oil upon the eyes he says: "This in my Opinion proceeds from some hot, sharp Particles, contained in the Oil . . . for I remember when at Montpellier, I was informed by Monsieur Magnol, and other of my Acquaintances there, that the feeding of tame rabbits with Olive

Leaves, in want of other food has caused their making bloody Urine." He says again: "I cannot charge myself with making the least mystery of my practice. For in Consultations in a number of Cases of Importance I have been always very free, and open; far from following the Example of some Physicians of good morals and great Reputation, who have on many occasions thought proper to conceal Part of their own acquired Knowledge, alleging the Maxim—*Ars est celare artem*." There were, so far as I can find, four editions of this book published. In 1746 it was translated into the French.

Sir Hans gave a strong impulse to the practice of inoculation by performing the operation upon several of the royal family. The following extract is from "An Account of Inoculation by Sir Hans Sloane, Bart.," published in the Philosophical Transactions, Vol. 49, p. 518:

Upon these trials, and several others in private families, the late queen, the princess of Wales (who with the King always took most extraordinary, exemplary, prudent and Wise care of the health and education of their children) sent for me to ask my opinion of the inoculation of the princesses. I told her royal highness, that by what appeared in the several essays, it seemed to be a method to secure people from the great danger attending that distemper in the natural way. That the preparations by diet and necessary precautions taken, made that practice very desirable; but that not being certain of the consequences, which might happen, I would not advise the making trials upon patients of such importance to the public. The princess then asked me, if I would dissuade her from it; to which I made answer, that I would not, in a matter so likely to be of advantage. Her reply was, that she was then resolved it should be done, and ordered me to go to the late King George the first, who had commanded me to wait on him upon that occasion. I told his majesty my opinion, that it was impossible to be certain but that raising such a commotion in the blood, there might happen dangerous accidents not foreseen: To which he replied that such might and had happened to persons, who had lost their lives by bleeding in a pleurisy and taking physic in any distemper, let never so much care be taken. I told his majesty I thought this to be the same case, and the matter was concluded upon and succeeded as usual without any danger during the operation or the least ill symptom or disorder since. . . . What I have observed, which I think material, is not to inoculate such as have any breaking out on their faces, soon after the Measles or any other occasion, whereby small-pox were likely to be invited, and come to the face in greater number and so make the distemper more dangerous. Bleeding in plethora or gentle clearing of the stomach and intestines, are necessary; and abstinence, from anything heating about a week before; and nothing else needful by way of preparation; and very little physic during the course of it, unless accidents happen.

The operation is performed by making a very slight shallow incision in the skin of the arm about an inch long; but great care should be had in making the incision not to go thro' the skin; for in that case I have seen it attended with very troublesome consequences afterwards. After the incisions are made, a dossil dipped in the ripe matter of a favorable kind of small-pox produced naturally or by inoculation, is put into the wound covered by diapalma plaster for twenty-four hours and then removed. . . . Upon the whole it is wonderful, that this operation, which seems so plainly for the public good, should, through dread of other distempers being inculcated with it, and other unreasonable prejudices, be stopped from procuring it.

In 1695 he married Elizabeth, daughter of John Langley, a London alderman, and widow of Fulk Rose of Jamaica. She bore him one son, Hans, and three daughters. In 1716 he was

created a baronet, being the first medical practitioner to receive an hereditary title. In 1722 he was made physician-general to the army.

In 1741 feeling the infirmities of his advanced age, he retired from service, left London and took up his residence at the old Manor House at Chelsea, which he had purchased in 1714. The house was a fine one, in what at that time was a charming suburb of London. It abounded in historical associations, the chief of which were those connected with Sir Thomas More.

In 1753, on the 11th of January, he died at Chelsea, at the age of 93. George Edwards, the naturalist, says: "He was so infirm as to be wholly confined to his house, except sometimes, though rarely, taking a little air in a wheeled chair. . . . The last time I saw him, I was greatly surprised and concerned to find so good a man in the agonies of death. He died on the eleventh, at four in the morning, being aged ninety-three. I continued with him later than any of his relatives but was obliged to retire, his agonies being beyond what I could bear; though under his pain and weakness of body, he seemed to retain a great firmness of mind and resignation to the will of God." He was buried in the church yard at Chelsea beside his wife, who died in 1724. Over his grave his daughters have erected a monument.

In 1748 a statue was erected to him in the Apothecaries' Garden at Chelsea. In the National Gallery in London there is a portrait of him; one belongs to the Royal Society and one hangs in the dining room of the College of Physicians. His memory is perpetuated by such names as Sloane Street, Sloane Square, Hans Place and Hans Road.

He had a large practice among the upper classes. Queen Anne consulted him; in one of his notes he tells how it took him four hours to drive to Windsor in his coach and four; in her last illness he advised that she be "blooded." Mr. Pepys, in writing to Captain Hatton, says "you give me hopes of your recovery from the care and knowledge of our friends Dr. Sloane and Mr. Barnard . . ." (Diary, IV, 298). Pope alludes to him in his *Moral Epistles* (IV, 10) when he says: "And books for Mead and butterflies for Sloane"! and in his *Satires* (VIII, 30) he says: "Or Sloane or Woodward's wondrous shelves contain." Young, in his *Satires* (IV, 113) says: "Sloane, The foremost toyman of his time."

Sir Hans was tall and well made, with easy, polite and engaging manners, sprightly in conversation and very obliging; he thus made friends and became well known, commanding the admiration and respect of all with whom he came into contact.

He was a very benevolent man, broad-minded and taking a deep interest in all the activities of his time. He gave his advice freely to those unable to pay; the rich and the poor he treated alike in giving them the best he had. He gave liberally, though carefully, to those in financial distress. He was one of the founders of the Foundling Hospital. In 1721 he founded for the Society of Apothecaries the Botanical Gardens at Chelsea. He gave the Royal Society 100 guineas and a bust of Charles II. In 1732 he became one of the promoters of the Colony of Georgia. He was a governor in most of the London

hospitals, and they all felt his influence. He loved wealth but did not make it subservient to his love for science. Indeed, he used much of his wealth in enriching the sciences he so dearly loved. Unless one can fully understand the social conditions under which Sir Hans lived and worked, it is not possible to estimate him at his true worth; for example, all that he did in his study of nature seems rather commonplace in the brighter light of to-day, but it was great in his time, when one possessed with a taste for collecting insects and the like was by the ablest men regarded as having a tendency to lunacy. He was a very painstaking man, or, as one writer puts it, he had an unweariable power of taking pains.

He seems to have been so busily occupied in doing his daily tasks that he had little time for recording the events of his life, and we cannot but regret that he has left behind such meagre accounts of himself and his activities. What interesting and instructive reading would a diary of his, similar to that of Gideon Wells, be; how much light it would throw upon the medical men of those days, and in a way that can only be obtained through the records of one who, like Dr. Sloane, was in close touch with the men and their activities.

Edwards speaks of him as follows:

The charities of human life were not, in the breast of Sir Hans Sloane, choked either by the various allurements and preoccupations of science or by the ceaseless toils of a busy and anxious profession. The multiplicity of claims was, indeed, as notable as was the patience with which they were listened to. Not to dwell upon the innumerable gropings after money, of which, in one form or another, every man who attains any sort of eminence is sure to have his share (but of which Sir Hans Sloane seems to have had a Benjamin's portion), or upon interminable requests for the use of influence—at court, at the Treasury, at the London hospitals, at the Council Boards of the Royal Society or of the College of Physicians, and elsewhere—his fame brought upon him a mass of appeals and solicitations from utter strangers, busied with the less worldly aims and pursuits. Enthusiastic students of the deep things of theology sought his opinion on abstruse and mystical doctrines. Advocates of perpetual peace and of the transformation, at a breath, of the Europe of the Eighteenth century into a Garden of Eden, implored him to endorse their theories, or to interpret their dreams. . . . To one of the enthusiasts in mystic divinity, who had sent for his perusal an enormous manuscript, he replied, "I am very much obliged for the esteem you have of my knowledge, which I am very sure comes far short of your opinion. As to the particular controversies on foot in relation to Natural and Revealed Religion and to Predestination, I am noways further concerned than to act as my own conscience directs me in those matters; and am no judge for other people. . . . I have not time to peruse the book you send." (Edwards' *Lives of the Founders of the British Museum*, Vol. I, p. 292.)

The same author says:

To the worthy and once famous Abbé Saint Pierre, who would fain have established with Sloane a steady correspondence on the universal amelioration of mankind, by means of a vast series of measures, juridical, political and politico-economical, which started from the total abolition of vice and of war, and descended to the improvement of road-making, by some happy anticipation, a hundred years in advance of our own macadam, he wrote thus: "I should be very glad to see a general Peace established forever. Rumors of war are often, indeed, found to be baseless, and the fears of it, even when well grounded, are often dissipated by an



unlooked for Providence. But poor mortals are often so weak as to suffer, in their health, from the fear of danger, where there is none." (*Ibid.*, p. 293.)

The British Museum owes its origin in great part, and some say altogether, to Sir Hans Sloane, and no review of his life is complete without a reference to that institution. In 1702 Dr. Sloane secured the collection of William Courten, in 1710 that of Plukenet, and in 1718 he bought the collection of John Petiver for £4000, so that in 1753 his library contained 3516 manuscripts, 347 drawing and 40,000 books. The Sloane manuscripts contain letters and notes by most of the chief physicians of the century preceding Sloane's death and must always be one of the main sources of medical history in England from the time of Charles II to that of George II.

He bequeathed his books, manuscripts, prints, drawings, pictures, medals, coins, seals, cameos, and other curiosities to the nation on condition that Parliament should pay his executors £20,000.

When the subject was presented to George II, he received it with indifference and dismissed the matter with the remark that he did not think there was £20,000 in the Treasury. No

money being available from the government, it was decided to raise the sum needed by a lottery: 100,000 shares at £3 each were authorized. Of the money thus secured £200,000 was allotted for prizes and £100,000, less expenses, were to be used in the purchase of the Sloane and Harleian collections and to provide a place for their safe keeping. A great scandal resulted from the traffic in tickets by one Leheup. "By this unfortunate episode, the name of one of the best of Englishmen was brought into a momentary connection with the name of one of the worst," so says a writer.

The bequest having been accepted and the money raised, the Sloane collection, together with that of George II's Royal Library, was opened to the public at Bloomsbury as the British Museum in 1759, six years after the death of Sir Hans.

As a fitting close, let me leave with you his counsel. "I advise you," he would say, "to what I practice myself. I never take physic when I am well. When I am ill, I take a little, and only such as has been very well tried."

The chief authorities consulted were Edwards' "Lives of the Founders of the British Museum" and Jardine's "Naturalist's Library."

## NOTES ON NEW BOOKS.

*Psychoanalysis.* By A. A. BRILL, Ph. B., M. D. (W. B. Saunders Co., 1913.)

The main object of this book is to present the practical application of Freud's theories in one volume in the hope of stimulating further interest in Freud's original works. The book consists of 325 pages divided into 12 chapters, dealing with, among other things, the Psychoneuroses, Dreams, Psychopathology of Everyday Life, Oedipus Complex, and Anal Eroticism and Character. The substance of the majority of these chapters has already been published in various medical journals, and consequently considerable repetition occurs throughout. The last chapter on Freud's theory of wit is prolix, and not by any means convincing.

Although some of the explanations and dream interpretations may be considered rather fanciful, still the author should be congratulated on having done his work so well, and for having presented such a difficult subject in a clear and concise way.

*General Paresis.* By PROFESSOR EMIL KRAEPELIN. Translated by J. W. MOORE, M. D. Journal of Nervous and Mental Disease, Monograph Series, No. 14. (New York: 1913.)

This is a translation of Kraepelin's article on general paralysis contained in the 8th edition of his text-book on psychiatry. The clinical descriptions are exceedingly detailed, and do not serve any specially useful purpose. There is nothing new or particularly enlightening about the article, and it is difficult to realize why its translation was undertaken.

*The Surgical Clinics of John B. Murphy.* M. D. Volume II. Number 2 (April, 1913). Illustrated. Published bi-monthly. Price per year, \$8.00. (Philadelphia and London: W. B. Saunders Company, 1913.)

This number of the *Clinics* furnishes the usual quota of remarks on a broad variety of surgical topics. We believe the *Clinics* would be more valuable were they grouped, so that one number

might be devoted entirely, for instance, to amputations, another to operations on the gastro-intestinal tract, etc. They seem to us more interesting as an exhibition of Dr. Murphy's wide versatility, than broadly educative to the reader unless he is already well trained in surgery.

*New and Non-official Remedies.* (Chicago: American Medical Association, 1913.)

This publication, first started in 1907, has grown yearly more and more important, and to-day there is no excuse for a general practitioner to prescribe any non-official remedy not included in this list. The committee of the association having the work in charge of examining these remedies is liberally inclined, and describes all on the market that are really valuable. The cheapness of this volume—only twenty-five cents in paper—brings it within the reach of all; and every member of the association should secure a copy and keep it close beside him.

*A Manual of Surgical Treatment.* By SIR W. WATSON CHEYNE, Bart., F.R.C.S., etc., and F. F. BURGHARD, M.S. (Lond.), F.R.C.S. New (2d) Edition. Thoroughly Revised and Largely Rewritten. \$6.00, net, per volume. (Philadelphia and New York: Lea & Febiger, Publishers, 1913.)

The fourth volume of this excellent work is arranged in four divisions: 1, The surgical affections of the jaws and tongue; 2, of the pharynx and oesophagus; 3, of the stomach and intestines; and, 4, of the rectum and anus. This is certainly the best English surgical manual, and one of the best in any language. When completed it will be a noteworthy addition to the extensive list of surgical treatises. All thorough students of surgery will be glad to have this work on their shelves. It is practical and authoritative; it is comprehensive but concise, and is a useful book for students.

# BULLETIN

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### OSTEITIS DEFORMANS, PAGET'S DISEASE.\*

#### A REPORT OF SIX CASES OCCURRING IN THE JOHNS HOPKINS HOSPITAL AND DISPENSARY.

By S. H. HURWITZ, M.D.,

*Medical House Officer, The Johns Hopkins Hospital.*

#### INTRODUCTION.

In the year 1816, Sir James Paget<sup>1</sup> presented before the Medical and Chirurgical Society of London a report on five cases of a "rare disease of bones." Six years later he was able to report seven additional cases to the same society<sup>2</sup> and by the year 1889,<sup>3</sup> he had seen 23 cases of this disease. Since his original communication, some 37 years ago, a large number of typical cases have been added to the literature; but osteitis deformans still remains a "rare disease of bones."

Higbee and Ellis<sup>4</sup> estimate that up to the year 1911 about 158 cases of osteitis deformans had been reported. This estimate is based upon the 66 cases collated from the literature by Packard, Steele, and Kirkbride.<sup>5</sup> During the 10 years following about 91 cases had been reported, 23 in this country and 68 cases abroad. In the two years, 1911 and 1912, I have found about 16 additional cases reported, of which approximately 10 are American. According to these figures about 175 cases of osteitis deformans are on record up to the present year.

It is of interest that the first case described in North

America was that of MacPhedran,<sup>6</sup> of Toronto, in 1885, nine years after Paget's original communication. Watson,<sup>7</sup> of Baltimore, in 1898, and Elting,<sup>8</sup> of Albany, in 1901, reported the seventh and eighth of the American cases in THE JOHNS HOPKINS HOSPITAL BULLETIN.

The number of cases of osteitis deformans noted in America has greatly increased since 1901. According to Higbee and Ellis, the total number of American cases had reached 33 in the year 1911. These added to the 10 cases which I have been able to find in the literature and the six cases included in this paper would make a total of about 50 American cases up to 1913.

Osler has seen about three or four cases in private practice, and Dr. E. A. Locke of Boston has kindly permitted me to mention that during the past 12 years he has studied, and recorded notes on 40 cases of osteitis deformans, and that about 20 or 30 more have come under his observation.

The present report includes six cases; three of these have been found in the records of over 30,000 medical admissions to The Johns Hopkins Hospital, and three in the much larger number of admissions to The Johns Hopkins Hospital dispensary. Although all of the six cases present essentially the features of the disease described by Paget, the compara-

\* Paper read before The Johns Hopkins Hospital Medical Society, May 5, 1913.

record. For the privilege of doing so I am indebted to Dr. L. F. Barker, in whose service these cases were studied.

## CLINICAL RECORDS.

**CASE I (Medical No. 30432).**—On February 17, 1913, J. P., a tailor, white, aged 77, was admitted to the medical service of The Johns Hopkins Hospital, complaining of inability to use his right hand.

**Family History.**—The patient was not aware of any unhealthy inheritance; in fact, his father and mother had both lived to be nearly as old as the patient himself. With the exception of one sister, who has tuberculosis, all of his brothers and sisters are well. The patient feels quite sure that neither of his parents was ever subject to "rheumatism," and that none of the members of his family had a similar affliction. He has 11 children, eight sons and three daughters, all of whom are well, except one daughter, who has tuberculosis.

**Personal History.**—Before his thirty-fifth year, the patient had suffered from several exhausting infectious diseases; aside from whooping-cough, measles, and mumps, he had scarlet fever in childhood. During adolescence he suffered from repeated attacks of malaria, and at the age of 35 had cerebrospinal meningitis which impaired his hearing.

The patient is a tailor, and has practiced his trade for about 60 years without interruptions due to ill-health. Except for an occasional winter cough, and a little shortness of breath, he could boast of excellent health until he was about 50 years old, when he began to suffer from intermittent attacks of pain in the right shoulder, and later in the right hip. He remained active, however, and continued at his work. He boasts that at this period he was as straight as a "shingle," and in strength the equal of any other man of his age. Upon inquiry as to his height at this period, it was learned that he stood 5 feet 7½ to 8 inches. He says that at 60, his legs were so straight that he could hold a coin between his knees or between his ankles.

**Present Illness.**—The patient paid little attention to his occasional "rheumatic" pains and felt quite unaware of any changes in the shape of his body until 10 or 15 years ago, when the members of his family began to notice that he was beginning to stoop, and that his legs were becoming bowed. The patient was then 62 years of age. He, himself, soon began to notice that he was losing in height; for being a tailor by trade he noticed that the inner seam of his trousers was becoming shorter. This measurement had decreased from 33¾ inches to its present length of 30½ inches. From a height of 5 feet 7½ to 8 inches, he has fallen to a height of 5 feet 2 inches, a loss of 5½ to 6 inches in about 10 or 15 years. He has noticed also that his waist measurement has increased from 24 to 34 inches. As for the size of his hat, the patient does not furnish very definite information. He used to wear a No. 7¼ hat and now finds a No. 7¾ a little small.

During the past few years, he has experienced a little awkwardness in the use of his legs: he finds some difficulty in separating them, and in placing one heel upon the opposite knee. In July, 1911, his ankles were swollen for a period of three weeks, and for the past few weeks he has had pain in his right hand. He has remained mentally clear and cheerful.

**Physical Examination.**—February 17, 1913. A general inspection of the patient immediately attracted the attention to the bony framework, which presented an unusual appearance. These alterations of the skeleton were most striking in the standing posture: a short, little man with a head which, though not in itself abnormally large, appeared definitely so when compared to the size of the body. The head is held slightly flexed over the chest; the latter is flattened in front, quite strikingly kyphotic

in the upper dorsal region, and flares below. The pelvis is unusually broad and feminine in type. The crests are heavy and nearly in contact with the lower ribs, producing a diamond-shaped abdomen with a pendulous wall. The extremities show interesting features: the arms appear unusually long compared to the height. Both legs are bowed above and below the knees, which are widely separated.

The head itself does not present the changes which are often so striking in these cases. It is somewhat triangular in shape, with the base of the triangle uppermost. The sutures and fontanelles are tightly closed. The face appears small in comparison with the calvarium, and excepting the nose, the features are not prominent.

The shape of the thorax and its peculiar distortion can best be appreciated from the cyrtometer tracing. The tracing was made at the level of the fourth dorsal spine and shows how the anterior and posterior median lines are thrown out of alignment. The antero-posterior diameter is 3 cm. less than the lateral diameter, the greater portion of which, 14 cm., lies on the side with the more marked kyphosis. Anteriorly, the thorax is flattened above, but the angle of Ludwig is prominent. The costal angle measures about 135 degrees.

The right clavicle presents a most unusual appearance. It is much thickened and roughened, although not nodular. There is an extreme accentuation of the normal curves. The ribs are also somewhat thickened and broadened and somewhat ankylosed to the articulating processes of the spine, thus greatly limiting the free movements of the thorax.

**Upper Extremities.**—The radius and ulna of each forearm is definitely bowed. This bowing is more marked on the left than on the right. No definite roughening or thickening of these bones can be made out.

The striking feature is bowing of both legs. The femora feel thickened and are bowed outward. The tibiae also are broader and thicker, but not roughened or nodular; the latter show both anterior and lateral bowing. The knees are slightly more prominent than normal. Both patellae are thickened, the left more than the right; the circumference of the left knee through the midpatellar region measures 36 cm., and that of the right 34 cm. With the patient lying flat in bed and the heels together, the distance between the two medial condyles is 11 cm. The difference between the measured length and the apparent length of the legs is 7 cm. on the right and 6.5 cm. on the left, due to the bowing and the shortening in Bryant's line. The shortening of Bryant's line points to a change in the angle between the neck and shaft of the femur, producing a coxa vara. This is well shown in the skiagram of the hip joint.

## MEASUREMENT OF PATIENT.

HEAD.		cm.
Occipitofrontal circumference (maximum).....		60.5
Occipitofrontal diameter .....		20.5
Occipitomenal diameter .....		20.0
Biparietal diameter .....		17.0
Suboccipito-bregmatic diameter .....		18.0
Suboccipito-bregmatic circumference .....		55.5
Bitemporal diameter .....		13.0
Circumference of vault, from meatus to meatus.....		37.0
THORAX.		
Antero-posterior diameter (tracing).....		23.0
Lateral diameter .....		26.0
PELVIS.		
Intercristal diameter .....		32.5
Interspinous diameter .....		30.0
Intertrochanteric diameter .....		32.0



UPPER EXTREMITY.		Right.	Left.
Length of arms (tip of acromion to styloid of radius) .....		54.0	54.0
Length of upper arm (tip of acromion to ext. condyle humerus) .....		30.5	30.0
Length of forearm (ext. condyle to styloid of radius) .....		27.0	27.0
Grand expansion of arms (66.2 inches), 165.5 cm.			

LOWER EXTREMITY.		Right.	Left.
Antero-superior spine to internal malleolus.....		83.5	84.0
Bryan's line .....		5.5	5.5
Great trochanter to ext. condyle of femur.....		41.0	42.0
Ext. condyle of femur to ext. malleolus.....		44.0	43.0
Circumference of knee (mid-patellar region).....		34.0	36.0

*Height*.—5 feet 2 inches. Height before onset of disease about 5 feet  $7\frac{1}{2}$  to 8 inches, a loss of  $5\frac{1}{2}$  to 6 inches. Calculated from the grand expansion of the arms the loss in height would be at least 4 inches.

*General Examination*.—Numerous lipomata over trunk and upper and lower extremities. No general glandular enlargement. Thyroid is not felt. *Lungs* show slight signs of emphysema. The conjunctival tuberculin test is negative. *Cardio-respiratory system*: cardiac dullness is not enlarged. Aortic second is ringing in quality. There is marked sclerosis of all the peripheral vessels, temporals, brachials, and radials. The blood pressure averages 140 (Tycos).

Examination of the fresh blood and of stained smears showed no abnormalities. The Wassermann reaction was negative.

Examination of the urine and feces showed no abnormalities. An ophthalmological examination showed a slight clouding of the lens in the left eye; both discs were well outlined; the arteries thin and tortuous; no hemorrhages or exudate on either fundus.

*Radiographical Examination* (Skiagram No. 17014. Reported by Dr. F. H. Baetjer).—*Skull* shows a uniform deposit of new bone, making the total thickness nearly one inch. Sella very irregularly shaped, but present. *Right tibia* shows no increased calcification, but a marked osteoporotic condition. *Left tibia* shows increased calcification especially on the anterior surface. There is also some osteoporosis confined largely to bone around medullary cavity. Both tibiae show well marked bowing. *Fibulae* both show longitudinal osteoporosis. *Pelvis*: heads of both femora are slightly bent, producing coxa vara; marked osteoporosis of necks and great trochanter; both ilia show osteoporosis in the bodies. Both pelvic bones show increased calcification, but no osteoporosis. Both femora are bowed. *Hand*: first phalanges all show marked porosis. The middle phalanges of index and fifth fingers show same condition; whereas those of third and fourth fingers show distinctly increased calcification. The third and fourth metacarpals are shorter than normal.

*Summary of Case I.* The chief features of this case are: First, the insidious onset of the disease at the age of 50 with vague rheumatic pains and its gradual progress until the age of 62, when the stooping of the body and the bowing of the legs had become well marked; thus the pains antedated the actual bony changes by about 10 years; second, the only slight discomfort to the patient produced by the gradually progressing deformity; third, the presence on examination, of the characteristic posture, the large calvarium, the bowing of the femora, tibiae, radius, ulna and the dorsal kyphosis and prominent right clavicle; fourth, the loss of  $5\frac{1}{2}$  to 6 inches in height; and fifth, the presence in the skiagrams of the typical bony changes of the disease.

*CASE II* (Disp. No. E.81938).—J.B., a white male, aged 74 years, first came to the Johns Hopkins Hospital dispensary about 10 years ago complaining of swelling of the legs. When seen again on March 16, 1913, the patient complained of "misery in the stomach, and shortness of breath."

*Family History*.—There is a suspicious tuberculous history among the immediate members of the family. The father died at the age of 42 of a "cold"; the mother died at about the same age of "congestion of the throat"; three brothers are all dead, one died at the age of 60, of pneumonia; one was crippled all of his life by a "white swelling of the hips and back"; and a third brother died at 24. Of two sisters who are dead, one died during childbirth, and the other of a "cold." The patient does not know of any heart disease, kidney disease, cancer or rheumatism in the family. He is not aware that any one in the family suffered from a deformity similar to his; except that his paternal grandmother became stooped between the ages of 50 and 60.

*Past History*.—The patient does not recall any diseases of childhood. In 1869, 44 years ago, he had typhoid fever and was ill for six weeks. He has always had a poor appetite, which has become worse during the past few years. He has been troubled with hemorrhoids for about 40 years.

In October, 1909, the patient returned to The Johns Hopkins Hospital dispensary complaining of constipation, headaches, and poor appetite. He states that he began to have a feeling of fullness and distention after eating, which has persisted up to the present time.

For about 10 years, the patient has suffered from swelling of the ankles; up to about five years ago, this edema was transient, but has been more constant since then. He has suffered from catarrh for about 40 years, and complains occasionally of a cough. For the past few years, he has become very short of breath. He has had nycturia for about 30 years and now complains of increased frequency of micturition.

*Present Illness*.—The patient has paid little attention to his gradually progressing deformity. In fact, during the last few years, he has attended the dispensary at irregular intervals but has not complained of the bowing of his legs, which according to the history notes, has been becoming more prominent.

Upon questioning the patient further, the latter states that about 20 years ago, when he was about 54 years old, his friends would tell him to straighten up, because he was getting "full-breasted" in the back. He thinks that his height at this period was about 5 feet 7 inches. He, himself, never noticed that his legs were becoming bowed, but he was told so by the doctor at this dispensary about 10 years ago. He has not paid any attention to changes in the size of his head, but thinks that he wears a larger hat now than formerly. During the past year the size of his hat has increased from No. 6½ to No. 7.

*Physical Examination*.—March 16, 1913. The patient is a short, stooped, emaciated old man of 74 years. His supraorbital ridges are prominent and his eyes appear sunken in their orbits. There is a well marked arcus senilis; the pupils react to light and on accommodation. The temporal arteries are visible and tortuous. Mucous membranes are somewhat pale. Tongue is furred. There are no teeth in either jaw.

The patient's head looks top-heavy. The calvarium is squarish in shape, and bulges in the frontal, occipital and parietal regions. Over these areas, as well as over the vertex, there can be felt a few rounded, nodular elevations. With the exception of the nose, the features are small in comparison with the size of the calvarium.

In the natural standing posture, he presents an unusual appearance. Viewed laterally, the deformity of the body resembles the shape of the letter S, the dorsal kyphosis contrasting markedly with the bending and forward bowing of the legs. The head is held forward, and downward, and the arms appear unusually long for the height.

The chest looks as if it had sunken into the pelvis, the costal margins and crests of the ilia being nearly in juxtaposition. The antero-posterior diameter of the thorax is slightly greater than

the lateral diameter. (The greatest kyphosis is at the level of the 6th dorsal spine.) The clavicles are not unusually prominent, but the supraclavicular fossae are deep. The angle of Ludwig is prominent, and the costal angle narrow. The ribs are closely approximated and feel slightly thickened. The spine is rigid and immobile.

The abdomen is diamond-shaped. Just below the costal margins there is a well marked transverse furrow, below which the abdomen is pendulous. The bony pelvis flares out and is broad and capacious. The iliac crests are thickened, measuring 3.5 cm. in width behind the antero-superior spines, and feel rough. The external lips overhang the iliac bones.

*Lower Extremities.*—The lower extremities are in a position of genu varum. With heels together the knees are separated 12 cm. from one another, as measured between the two internal condyles of the femora. Both femora are bowed outwards and slightly anteriorly, the left more than the right. The bones feel a little thickened and roughened. Due to the extensive edema of the legs, the lateral bowing of the tibiae is not apparent, but the anterior bowing is very pronounced. There is also some irregularity and thickening of both tibiae. Feet are not involved.

*Upper Extremities.*—Both humeri feel thickened in the upper third, but no definite bowing can be made out. The radius and ulna on each side are definitely bowed, the left more than the right. The surfaces of these bones are not thickened or roughened. Fingers are small and narrow. Soft parts not increased.

## MENSURATION OF PATIENT.

## HEAD.

Occipitofrontal circumference (maximum).....	58.0
Occipitofrontal diameter .....	17.5
Occipitomenital diameter .....	23.0
Biparietal diameter .....	15.0
Suboccipito-bregmatic diameter .....	17.0
Suboccipito-bregmatic circumference .....	55.0
Bitemporal diameter .....	13.5
Circumference of vault, from meatus to meatus.....	36.0

## THORAX.

Circumference: sixth dorsal spine.....	81.0
Antero-posterior diameter (tracing).....	26.0
Lateral diameter (tracing).....	25.0

## PELVIS.

Intercristal diameter .....	31.0
Interspinous diameter .....	28.0
Intertrochanteric diameter .....	31.5

## UPPER EXTREMITY.

	Right.	Left.
Length of arms (tip of acromion to styloid of radius) 56.5	54.5	
Length of upper arm (tip of acromion to ext. condyle of humerus) .....	33.0	32.0
Length of forearm (ext. condyle to styloid of radius) 26.0	25.0	
Grand expansion of arms (66 inches), 167 cm.		

## LOWER EXTREMITY.

Antero-superior spine to internal malleolus.....	81.5	80.0
Bryant's line .....	6.0	5.5
Great trochanter to ext. condyle.....	44.5	42.0
Ext. condyle to ext. malleolus.....	40.5	39.5
Circumference of leg (mid-patellar region).....	35.0	37.0
Circumference of leg (15 cm. below patellar region) .	34.5	35.0
Circumference of leg (ankle).....	23.0	25.0

*Height.*—4 feet 11¾ inches. Height before onset of disease, 5 feet 7 inches, showing a loss of 7¾ inches. Recorded height in

April, 1910, is 5 feet 1¾ inches, showing a loss in two years of 2 inches. Calculated from the grand expansion of the arms, the loss in height is estimated at 6¼ inches.

*Visceral Examination.*—*Lungs:* thorax expands as a whole, the upper left front a little more than the right. Vocal fremitus is well transmitted over both lungs in front; the percussion note is hyperresonant; slight impairment at apices. Breath sounds are emphysematous in type and inspiration is accompanied by a few fine crackles. Tuberculin conjunctival test, both 1 per cent and 5 per cent negative.

*Cardiovascular.*—Visible pulsation in fifth intercostal space. No shock or thrill. Cardiac dullness begins over third rib and extends 11 cm. to the left and 5 cm. to the right over the fourth rib. At the apex the first sound is followed by a short systolic murmur, transmitted to the axilla. Sounds at base are clear and of equal intensity. Pulse is regular, small volume. Radials and brachials are beaded and hardened. Blood pressure 180 (Tycoos).

Urine shows a trace of albumin.

*Abdomen.*—Breathing is chiefly abdominal due to, more or less, ankylosis of ribs. The abdominal walls are soft. There is slight tenderness in the epigastrium on deep palpation. Liver dullness reaches just to costal margin. Spleen and kidneys are not palpable.

*Genitalia.*—There is enlargement of both external inguinal rings with definite impulse on coughing.

*Reflexes.*—Present in both upper and lower extremities.

*Radiographical Examination* (Skiagram No. 17297. Reported by Dr. F. H. Baetjer).—*Skull:* sella normally shaped; of solid type. Bones show uniform thickening; thickening is symmetrical and not so irregular as in Case I. Thickness one-half inch.

*Tibia and Fibula* (left).—Tibia markedly bowed anteriorly, and irregularly thickened with longitudinal areas of porosis. Fibula shows very little increased calcification, but on the contrary, large areas of longitudinal porosis. The right tibia shows the same condition, but to a less degree.

*Summary of Case II.*—Certain points in the history of this case are deserving of special mention: First, the slow painless progress of the disease. The disease began at the age of 54, but the patient did not complain of any symptoms until 10 years later; then he sought medical aid, not for his deformity about which he was practically unaware, but for the symptoms of myocardial insufficiency, due to the embarrassment of the circulation by a deformed thorax; second, the case illustrates, in an unusual way the typical changes in the skeleton wrought by osteitis deformans: large square head, marked kyphosis, bowing of both femora and tibiae; third, the loss of 7¾ inches in height; fourth, the skiagrams of the case show excellently the changes in the long bones, the porosis and calcification so characteristic of this disease.

*CASE III* (Disp. No. E. 86138).—R. W., white, aged 53, came to the orthopedic division of The Johns Hopkins Hospital dispensary in 1912, complaining of pain in "both hips, right knee, and right shoulder."

*Family History.*—The patient's family history is of interest since there is some evidence that the mother of the patient was similarly afflicted. His mother lived to the age of 87 years. Up to the age of 50 or 60 her health was good. At this time she began to complain of "rheumatism." These rheumatic pains were associated with swelling and bowing of the legs. According to the account of the patient's wife, "mother and son were the image of one another." Aside from the patient's mother, no other members of the family had any similar trouble. The patient's father died at the age of 62 years of a "chronic cough." One brother and one sister died in middle life. There is no history of heart disease, nephritis, or malignant disease in the family.

**Past History.**—The patient can boast of good health until the onset of the present illness. He cannot recall any diseases of childhood. His birth was normal and his development uneventful. He is quite sure that he was a well nourished baby without any of the stigmata of rickets. There is no history of any infectious diseases during adolescence and manhood. He has had periods of shortness of breath and palpitation. Denies gonorrheal and luetic infections. The patient has three healthy children and his wife has never had any miscarriages.

About 15 years ago, the patient received an injury to his right ankle which disabled him for six weeks. After recovering, he did not notice any difference in the usefulness of his right leg.

**Present Illness.**—It is difficult for the patient to state definitely when the changes in his body began. About 10 years ago, when the patient was 42 years old, he began to suffer pain in his right hip, and right leg. Both of his legs became swollen and the patient's wife noticed that his right leg was beginning to bend. Later the left leg became bowed. A few years after the onset of his illness, the patient came to this dispensary for treatment and after a long absence, returned in February, 1912. The pains in his hips have continued to the present time. Now, he complains also of cramp-like pains in the calves of his legs, which keep him awake at night. Both his right knee and right shoulder have become painful. For the past five years he has had transient oedema of the ankles and feet; this is gradually becoming more constant.

For the past 10 years his friends have noticed that he was becoming stooped and deformed. From a height of 5 feet 7 inches, at the age of 38, he has fallen to his present height of 5 feet 3½ inches, a loss of 4 inches. The right leg, where the bowing started, has progressed more than the left in this process, so that it is now considerably shorter than the left. To equalize this difference in length of the two legs, the patient must wear a higher heel on the right shoe. During the past six years the patient himself has noticed that he was buying larger hats. A cap worn by the patient six years ago measures 6½, whereas the patient now wears a No. 7¼.

The patient is a driver of a delivery wagon. In spite of his affliction, he still finds it possible to continue his work. He does, however, feel more clumsy and awkward than formerly in the use of his legs, especially in getting on and off the wagon.

His general health has remained good, and although he has become depressed on account of his condition, there is not the slightest evidence of any mental deterioration.

**Physical Examination.**—March 9, 1913. The patient is an undernourished man of 54. His stunted appearance, heavy head, and bowed, waddling legs immediately attract the observer's attention. Aside from a little looseness of the skin, a slight pallor and some pyorrhea and dental caries, there is little of importance in the general survey.

The attitude of the patient, while standing, is almost pathognomonic of the disease: the body is small and stooped, the legs are markedly bowed, laterally and considerably anteriorly. The head appears out of all proportion to the size of the body. One gets the impression that the weight of the head has produced an anterior bowing of the cervical spine. This enlargement of the head is entirely of the calvarium, especially in the parietal and occipital regions. The features are not accentuated; the lower jaw does not protrude.

The thorax shows a well marked kyphoscoliosis in the mid-dorsal region, the convexity of the scoliosis being slightly more to the left. The right clavicle is more prominent than the left, though this difference is not striking. There is considerable flaring of the thorax below, producing a wide costal angle (about 120°).

The abdomen is slightly prominent and there is no well defined furrow separating it from the thorax above. It is definitely

wider laterally than is normal. So that the distance from ensiform to symphysis pubis about equals the lateral diameter between the two anterior superior spines. The pelvis is feminine in type, being broader, flatter, and thicker than usual. The iliac crests are broad and thick; the external lip is accentuated and overhangs the bones.

**Lower Extremities.**—Both legs are markedly bowed, due to the outward bowing of both femora and tibiae; this bowing is more marked on the right. There is well developed anterior bowing of both tibiae. The right leg is definitely shorter than the left, the internal malleolus on the right side being 4 cm. higher than on the left. The knees are in a position of genu varum. With the heels together, the knees are separated a distance of 9 cm. as measured between the two internal condyles. Both patellae are slightly thicker than normal.

The tibiae feel thick, coarse, and nodular. Well marked oedema of the ankles is present on both sides. No oedema is present on the dorsum of the feet. The toes appear normal and the feet show no changes.

**Upper Extremities.**—The arms, except for their appearance of disproportionate length, are apparently only slightly affected. Both humeri feel a little roughened in the upper third. There is no change in the radius and ulna of the right arm. The radius on the left is slightly bowed. Hands are small and pudgy. Fingers short and thick. No signs of bony deformity or thickening.

#### MENSURATION OF PATIENT.

##### HEAD.

Occipitofrontal circumference (maximum).....	59.0
Occipitofrontal diameter .....	20.0
Occipitomenital diameter .....	22.0
Biparietal diameter .....	15.5
Suboccipito-bregmatic diameter .....	19.5
Suboccipito-bregmatic circumference .....	54.5
Bitemporal diameter .....	12.0
Circumference of vault from meatus to meatus.....	38.0

##### THORAX.

Circumference (sixth dorsal spine).....	83.6
Antero-posterior diameter (cyrtometer tracing).....	23.0
Lateral diameter .....	30.0

##### PELVIS.

Intercristal diameter .....	29.0
Interspinous diameter .....	25.5
Intertrochanteric diameter .....	32.0

##### UPPER EXTREMITY.

	Right cm.	Left cm.
Length of arms (tip of acromion to styloid of radius).....	56.0	54.5
Length of upper arm (tip of acromion to ext. condyle of humerus) .....	30.5	22.5
Length of forearm (ext. of condyle of humerus to styloid of radius).....	25.5	20.5
Grand expansion of arms (68 inches), 173.5 cm.		

##### LOWER EXTREMITY.

Antero-superior spine to internal malleolus.....	82.5	84.5
Bryant's line .....	4.0	5.5
Great trochanter to external condyle.....	40.0	40.5
External condyle to external malleolus.....	41.5	40.5

**Height.**—Present height is 5 feet 3½ inches. Height before onset of disease 5 feet 7¼ inches, which corresponds approximately to the measurement of the grand expansion of the arms, showing a loss of about 4 inches in height.

**Visceral Examination.**—Lungs: thorax expands only slightly on deep inspiration. Breathing is chiefly diaphragmatic. Percus-



sion note is hyperresonant; breath sounds are emphysematous in type. *Heart and Vessels:* apex beat can be well localized in fifth intercostal space, in the mammillary line. Cardiac dullness begins over the third costal cartilage and extends 11 cm. lateral to mid-sternal line in fifth intercostal space and 4 cm. to the right over the fourth rib. Cardiac action is irregular. At the apex the first sound is followed by a faint systolic bruit, not well transmitted. At the base both sounds are clear. Pulse is of large volume, very irregular in force and rhythm. Temporals, radials, and brachials are tortuous and sclerosed.

Blood pressure 125 (Tyco).

*Abdomen.*—The abdominal walls are soft. No generalized or localized tenderness. Liver dullness ends at costal margin. Liver and spleen are not felt.

*Reflexes.*—Present in both upper and lower extremities. Normal plantar response.

*Radiographical Examination* (Skiagram No. 12562. Reported by Dr. F. H. Baetjer).—*Skull* shows thickening of inner and outer tables with flocculent deposits of bone, irregularly placed over the entire outer table. Sella turcica is slightly enlarged and of solid type. *Tibia* shows marked thickening, especially of the anterior surface with small areas of porosis. *Femur* shows the same condition.

*Summary of Case III.*—It is of interest that in this patient the disease began in the fifth, rather than in the sixth decade, as in the two previous cases. The symptoms of onset, as in Case I, were vague rheumatic pains in the right hip and right leg, the latter being the first involved in the bowing. The skeletal parts show the usual changes with a marked increase in the circumference of the head and the loss of about four inches in height. The history of trauma to the right ankle, five years before the onset of the first symptoms, calls for the mention of injury as an etiological or predisposing cause. Several of the recorded cases, including Paget's original case, and that of Packard, Steele, and Kirkbride, gave a history of trauma.

If the patient's account be correct, and if one can rely on photographs, the mother of the patient began to develop the disease at the age of 60. This is of interest in connection with the view that heredity is an important factor in the etiology of this affliction.

*CASE IV\** (Medical No. 13120).—O.W.S., white, a carpenter, 59 years old, was admitted to the medical service of The Johns Hopkins Hospital on July 10, 1901, complaining of dropsy, dimness of vision, and stomach trouble.

*Family History.*—The patient's father died of old age, and his mother died of heart disease. For years before her death, the patient's mother suffered from rheumatism. There is no history of gout, cancer, or tuberculosis among the members of the family.

*Past History.*—The patient cannot recall any diseases of childhood. Excepting small-pox in the year 1859, no mention is made in the history of any illness until 25 years ago, when the patient had a sun-stroke. At this time, he was ill for several months and thinks that his whole system suffered considerably from the shock. For about 15 or 20 years he had suffered from dyspepsia and attacks of diarrhoea, and was very susceptible to any indiscretion in diet. During the past few years, he has complained of a weak back and irregular attacks of "rheumatism," which, however, have not incapacitated the patient from his usual work.

The changes in the shape of his body had scarcely attracted his attention, although he had noticed that his hat was one-half inch larger in size, and that the bones of his legs were thicker, and his back more bowed. At the time of admission, he was three inches shorter than formerly.

\* Both Cases IV and V are mentioned by Emerson in his article on Paget's Disease in Osler's Modern Medicine, 1909, VI, 717.

*Habits.*—The patient has been a hard worker at his trade. He does not use alcohol, but has smoked and chewed all of his life.

*Present Illness.*—One year before admission, when the patient was 58 years of age, he began to have lassitude, weakness, shortness of breath on exertion, and quite general oedema. Three months ago he had his first syncopal attack: sudden loss of consciousness and dimness of vision, lasting for 20 minutes, followed by diplopia, tinnitus and giddiness. Nycturia and polyuria now became troublesome symptoms: the patient has had to void about every two hours, and has noticed that the color of his urine is darker.

For the past two months he has had diarrhoea, and has lost about 35 pounds in weight. More recently he had been troubled by stiffness in the muscles of his neck, and pain in the back of his head and over the left eye.

*Physical Examination.*—The patient is a sparsely nourished man. The striking features on examination are the osseous changes: the head is unusually large for the size of the body, the enlargement being most striking in the occipital and parietal regions. The circumference of the head about the brow measures 59 cm.; the antero-posterior diameter is 21 cm., the lateral diameter 17 cm. With the exception of the bridge of the nose, which is unusually broad, the bones of the face show no changes.

*Thorax.*—The neck is short and the head is closely set on the thorax. There is a marked pigeon breast and a high grade of dorsal bowing of the spine. The most marked kyphosis is in the upper dorsal region, so that the antero-posterior diameter at this point is increased, being 25 cm. as compared to a lateral diameter of 21 cm. The thorax, which is narrow above, flares markedly at the costal margin. Both clavicles are unusually prominent and bowed.

The *abdomen* is much foreshortened in the vertical diameter, the space between the costal margins and iliac crests being about a finger's breadth. There is a transverse furrow below the margin of the ribs.

*Extremities.*—There is marked atrophy of the muscles about the shoulder girdle, and considerable muscular weakening of the upper and lower extremities. The patient is unable to completely extend the forearm on the arms. Both humeri are practically normal. There is a definite bowing of the ulna and the radius on both sides. No epiphyseal thickening can be made out.

Both femora are markedly bowed outward. Both tibiae show distinct bowing outward and forward. There are no localized nodular thickenings along the course of the long bones and no areas of tenderness.

The patellar reflexes are active on both sides.

The general examination showed only marked arteriosclerosis, slight cardiac enlargement, and a little bronchitis and emphysema. There was little evidence of heart disease. In the urine, there was a trace of albumin, but no casts.

Examination of the eye grounds showed no abnormalities in the fundi.

*Summary of Case IV.*—In this case, as in Case II, the symptoms which brought the patient to the hospital were dependent upon arteriosclerosis and myocardial degeneration, and had no direct relation to the disease. The onset had evidently been so insidious and the evolution of the disease so slow and gradual that the patient had little knowledge of the changes in his bony framework. For this reason, it is difficult in this case to determine the exact age of onset, though Emerson, in referring to this case, placed it at 58.

*CASE V* (Medical No. 20609).—T.P.H., white, a potter, aged 67, was admitted to The Johns Hopkins Hospital on January 7, 1907, complaining of "asthma."

*Family History.*—The father of the patient died of sun-stroke at the age of 66 years. The patient's mother died of pneumonia at 62 years. One brother died when young. Two sisters of the

patient are alive and well. The patient feels certain that no other members of his family have had any deformities similar to his. Both his father and grandfather were erect until the day of their deaths. The patient's father suffered from rheumatism.

*Past History.*—The patient has always been a strong, and fairly well man. He had rheumatism when 16 years of age, but has had no attacks until his recovery from "chills and fever" 16 years ago, when the patient was 51 years old, since which time he has had "rheumatism" in various joints. Of late, he has had headaches. His vision has been failing for the past year, and about one and one-half years ago he began to be deaf. The "asthma," of which he complains, came on insidiously and comes and goes. He has had no gastro-intestinal disturbances until five or six years ago, when he began to have poor control over his anal sphincter. Of late he has lost entire control of his bladder and rectum.

*Present Illness.*—For the past year the patient has been unable to work. The asthmatic attacks, which began insidiously, have grown gradually worse. He has a tight feeling in the chest with very little sputum and no pain on coughing.

The patient apparently knows very little of his deformity. Upon closer questioning it was learned that the first change in his stature began after his attack of "malaria," 16 years ago, when the patient was 51 years old. The beginning of these changes was associated with "rheumatism." It was about this time that the patient's sister noticed the change in her brother's height.

*Physical Examination.*—The bones of the cranium are greatly enlarged, the enlargement involving especially the frontal, temporal, parietal, and occipital bones. The bones feel normal and present no fossæ. There is no enlargement of the bones of the face, which is small in comparison to the calvarium. The eyes are small and appear tucked under a large brow.

The following are the measurements of the head:

Bitemporal diameter .....	40.00
Biparietal diameter .....	18.00
Occipitofrontal diameter .....	19.25
Circumference in O. F. diameter.....	60.00
Occipitomenital diameter .....	19.75
Suboccipito-bregmatic diameter .....	19.00
Circumference in S. O. B. diameter.....	50.00

Thorax is greatly deformed and asymmetrical. A marked kyphosis and scoliosis, mainly in the mid-dorsal region constitutes the essential deformity. The convexity of the scoliosis is to the right, producing a bulging of the thorax on the right side, and a corresponding flattening on the left side. The flaring at the costal margins produces a wide epigastric angle. The clavicles are prominent. The circumference of the thorax at the top of the axilla measures 85 cm. of which the right side measures 44 cm. The antero-posterior diameter measures 28.1 cm., whereas the lateral diameter measures 26.1 cm.

There is some bowing of the radius, ulna, and humerus, with the concavity backwards. This bowing is much more marked in the left radius. The long bones of the lower extremities are markedly deformed. Both femora are bowed and the tibiae have an outward and anterior curve. Both ankles are edematous.

The estimated height of the patient at the age of 27 is 5 feet 8 inches as compared to a height of 4 feet 6¼ inches on admission, showing a loss of 13¾ inches in stature.

Examination of the lungs and cardio-vascular system showed little more than signs of emphysema, chronic bronchitis, and advanced arteriosclerosis. A systolic murmur heard at the apex is transmitted to the axilla. The urine showed no albumin or casts. The blood pressure averaged 145 mm.

The ophthalmological examination showed a streak of opacity in the right cornea and cataracts in both eyes.

On examination, the blood showed a slight anæmia and a differential count of stained smears showed a fairly normal percentage of the different cellular elements.

*Summary of Case V.*—This case belongs with Cases I and III, to the painful group. The disease began at the age of 51 with "rheumatic" pains in various joints and bowing of the legs. The loss of height in this case is far greater than in any of the other four cases; it is estimated that the patient lost over a foot during the evolution of the disease.

*CASE VI.*—After the preparation of the previous cases, I had the opportunity to observe an excellent instance of this disease in a colored man. This patient (C. B., Dispensary No. F. 4702), aged 61, came to The Johns Hopkins Hospital dispensary on April 7, 1913, complaining of pain in his right knee.

*Family History.*—The patient gives a negative family history: his father died when the patient was quite young; his mother lived to be 68 years old and was erect to the time of her death; none of his brothers or sisters was deformed.

*Past History.*—The patient, himself, has been unusually well all his life. He says that his legs were not bowed when he was a child. With the exception of measles and typhoid fever, he does not recall any infectious diseases. There is a history of repeated gonorrheal infections, but the patient denies having had lues.

*Present Illness.*—The present illness began 15 years ago, when the patient was 46 years old, with pain in the right knee and "rheumatism" in his right leg. Soon after the onset of these symptoms, his right leg began to weaken and to bend. According to the patient's account, the left leg remained unaffected until eight or nine years ago, when it too began to bend. He does not know whether his head has changed in size. At present he wears a No. 7½ hat. The patient knows that he has gotten much shorter, but he cannot say how much he has lost in height.

In February of this year, the patient fell on his right knee. Since this accident he has been very much disabled. His rheumatic pains have become greatly aggravated and he can walk only short distances and then only with the aid of a cane.

*Physical Examination.*—April 19, 1913. The patient is a deformed, crippled, and dwarf-like colored man whose general posture is unusually simian in character. One is immediately struck by the enormous head and the extreme bowing of both legs. The head measures 64 cm. in its greatest circumference; the occipitofrontal diameter measures 21 cm. and the biparietal diameter measures 17 cm. The distance from tragus to tragus measures 43 cm. In this case, the enlargement of the calvarium in the parietal, occipital, and frontal regions is more striking than in the first three cases which I have been able to study. There is a large boss about the size of a hen's egg in the right frontal region. The face below the huge calvarium appears diminutive in comparison. The features are not enlarged.

Both lower extremities are bowed to such an extent that with the heels together, the distance between the two medial condyles of the femora measures 30 cm. The right leg is shorter than the left, but the latter shows more anterior bowing of the tibia. Both femora feel heavy and thickened; both show some outward bowing. The tibiae are enormously thickened, nodular, and slightly tender on firm pressure. The anterior bowing is much more striking in this case than in the first three cases. The lower third of the left tibia is heavier, coarser, and shows the most anterior bowing.

In the upper extremities no marked changes are demonstrable. There is, however, obvious bowing of the left radius, and slight bowing of the right radius.

The thorax is emphysematous in type, the clavicles are a little thickened, but not strikingly so. There is no kyphosis or scoliosis of the spine.

The abdomen is full and shows no transverse furrow. The pelvis is not exceptionally wide, the measurement between the antero-superior spines and that between the iliac crests being 27.5 and 28 cm., respectively. Due to the marked bowing of the legs, the distance between the trochanters is increased to 35 cm.

*Height.*—The patient thinks that he was 5 feet 6 inches before the onset of his deformity. The grand expansion of the arms measures 69 inches. His present height is 61 inches. According to these figures he has lost between 5 and 8 inches in height.

*Radiographical Study* (Skiagram No. 17517. Reported by Dr. F. H. Baetjer).—There is osteoporosis of the head of the tibia with areas of bony thickening; the entire tibia is enlarged. The femur shows marked thickening, but no osteoporotic areas.

The patella is thickened and shows osteoporotic areas. There is a formation of osteophytes along the edge of the articular surface of the tibia, some of which have been broken off and are lying loose in the joint.

Skiagrams of the skull were not obtained.

### HISTORICAL.

It is of some historical interest that studies of the skulls and bones collected in various archaeological museums of the world would seem to indicate that the disease existed even in prehistoric days. Paget,\* himself, made a careful study of the descriptions of large, thick, and porous skulls found in various museums. From a large number of specimens, many of them improperly classified, he was able to collect a group which are examples of true osteitis deformans. In 1885, Butlin<sup>10</sup> concluded from a study of the Neanderthal skull, thought by some to be rachitic, that the specimen belongs to the diseased condition now known as osteitis deformans.<sup>†</sup> From a study of Indian skulls and bones, Stegmann,<sup>11</sup> was able to report its presence frequently among the specimens observed. Wilks,<sup>12</sup> in 1857, observed some old specimens of this disease in the museum of Guy's Hospital. Recently, Waterhouse,<sup>13</sup> described a collection of bones dating from the year 1868, nine years before Paget's first communication, which are undoubtedly specimens from a case of osteitis deformans. This collection, presented to the Royal United Hospital in Bath by R. T. Gore, then surgeon to the hospital, is "from a man, aged 60, the subject of rickets in early life," and comprises a skull, scapula, clavicle, two humeri, a radius and ulna, femur, tibia, and fibula. These bones show very typical changes wrought by the disease which now goes by the name of osteitis deformans.

As a clinical entity, however, osteitis deformans is a disease of modern times. Certain cases reported prior to those of Paget as partial or local osteomalacia may have been atypical cases of the disease; as for instance, the cases mentioned by Paget: those by Saucerotte in 1801. Rullier in 1812, and Scoutetten<sup>14</sup> in 1841; whereas the cases described by Wrany in 1867, and by Wilks<sup>15</sup> in 1869 are considered by Paget, himself, as typical examples of the disease bearing his name.

\* Ref. 1, p. 61.

† Jonathan Hutchinson (Illus. Med. News, 1889, II, 177) refers to a portion of a parietal bone taken from an Egyptian tomb and now in the museum of the College of Surgeons, which would appear to be a good specimen of osteitis deformans, and as such probably the most ancient on record.

The case of Wilks included by Paget as one of his five cases is probably the first good clinical picture of the disease recorded in the English language. The report of Wilks is entitled a "Case of osteoporosis, or spongy hypertrophy of the bones (calvaria, clavicle, os femoris, and rib, exhibited at the Society)." This communication was published in the Transactions of the Pathological Society of London, for 1869. In this report Goodhart, then house physician to Guy's Hospital, included an autopsy record of the disease in which he calls attention to some of the important pathological changes in the bones. Wilks,\* <sup>12</sup> in a letter to the *Lancet* in 1909, modestly calls attention to his description of the disease, and says that because he could find no new osseous tissue, he was not inclined to regard the condition as resulting from an inflammatory process.

Czerny,<sup>16</sup> in 1873, first introduced the term osteitis deformans for a case of rather acute inflammation of the lower part of the tibia and fibula occurring in a soldier 22 years of age, and associated with softening, bending, and hardening of the bones. A year later, Schmidt<sup>17</sup> and Volkmann<sup>18</sup> both used the term, the former in connection with a case of spontaneous development of curvatures of the tibia and femur, and the latter for a similar case in which the curvature was confined to the tibia. Whether these cases are to be regarded as cases of true osteitis deformans in the sense of Paget is still disputed. Paget,<sup>†</sup> himself, was not inclined to class Czerny's case with those described by him, and Fitz, in this country, is inclined to the view that "multiplicity of the bones affected is the constant characteristic."<sup>‡</sup>

Notwithstanding that much was known and written about osteitis deformans before Paget's description of the disease, we owe to him a masterly account of its important clinical and pathological features, as well as a differentiation of this affection from a host of other osteopathies: Osteoporosis, osteomalacia, rickets, and various forms of hyperostoses.

### CLINICAL PICTURE

Some of the most important clinical features of the disease already have become apparent from the case records I have given. Paget's own description is so concise that I should like to quote him in this connection. In his original communication, he says of the disease:

"It begins in middle age or later, is very slow in progress, may continue for many years without influence on the general health,

\* Ref. 12. He says: "I called the case 'osteoporosis' or spongy hypertrophy of the bones. I so named it because it was the word on the labels attached to some old specimens in the museum at Guy's, and which evidently belonged to a case of this disease, shown by the enormously thickened skull and the large, crooked, long bones of the limbs. In giving my lectures in 1857, I commented on these bones and said I did not think they arose from an inflammatory process because I could find no new osseous tissue, either on their surface or interior, and therefore, I considered the name to be most excellent. When, therefore, an example of the same disease came under my own notice, I called it 'osteoporosis,' and more especially as I discovered no new osseous tissue either as ostitis or periostitis."

† Ref. 2, p. 225.

‡ Ref. 20, p. 401.



and may give no other troubles than those which are due to the changes of shape, size, and direction of the diseased bones. Even when the skull is largely thickened, and all its bones exceedingly altered in structure, the mind remains unaffected.

"The disease affects most frequently the long bones of the lower extremities and the skull, and is usually symmetrical. The bones enlarge and soften, and those bearing weight yield and become unnaturally curved and misshapen. The spine, whether by yielding to the weight of the overgrown skull, or by change in its own structure, may sink and seem to shorten with greatly increased dorsal and lumbar curves; the pelvis may become wide; the necks of the femora may become nearly horizontal, but the limbs, however misshapen, remain strong and fit to support the trunk. In its earlier periods, and sometimes through all its course, the disease is attended with pains in the affected bones, pains widely various in severity and variously described as rheumatic, gouty, or neuralgic, not especially nocturnal or periodical."\*

Some of these clinical features have been emphasized by more recent writers. Latzko<sup>20</sup> maintains that the non-conformity between the anatomical changes in the skeleton and the retained ability to walk is pathognomonic of the disease. Fitz<sup>21</sup> emphasizes the multiplicity of the bones involved as a characteristic feature.

Later reports seem to indicate that the disease is not necessarily symmetrical. The disease may be more developed in the bones of one side of the body than in those of the other; or there may be a crossed involvement, as in the case of Levi<sup>22</sup> (a woman 62 years of age) in which the bones affected were: Left humerus and right radius; right femur and left fibula; whereas, both tibiae were uninvolved.

Studies of the reported cases show that the skull, although the last to be involved, most frequently participates in the process, and that after the skull, the tibiae are the bones most often affected. The latter are followed by the femora, pelvis, spine, clavicles, ribs, and radii.

Contrary to Fitz's assumption, Schirmer<sup>1,23</sup> concludes from his collective study of the disease that there is a so-called "mono-osteitic" form, which for years may be confined to one bone, especially the tibia. In this group, Schirmer includes the cases reported by Schlesinger, Katholicky, Ménétrier and Gauckler, Schmieden and Symmonds.

According to the reported statistics, the occurrence of all of the six cases of this report in males would appear to be a mere coincidence. Most of Paget's 23 cases occurred in men. Of the cases collated by Packard, Steele, and Kirkbride,<sup>1,c</sup> in which the sex was stated, 41 were in men, and 24 in women, that is 61 per cent of the cases occurred in males and 35 per cent in females. The more recent statistics of Schirmer,<sup>1,c</sup> however, would seem to indicate that the disease was just as common in women as in men. Of 86 cases studied by him, 46 were in men and 40 in women.

With the exception of Cases III and VI in which the disease began in the fifth decade, in the four remaining cases the age of onset, as far as could be determined, was in the sixth decade. This corresponds closely to the age of onset of

the largest number of recorded cases. Of the 86 cases analyzed by Schirmer, 28 cases came under observation between the ages of 50 and 60, and 25 between the ages of 60 and 70. In about 61 per cent of these cases the disease reached its full development in the sixth and seventh decades. In some of these cases the disease undoubtedly began earlier and of 25 cases in which the age of onset was stated, 17 began in the fifth and sixth decades. From these figures, it is obvious that osteitis deformans is a disease chiefly of old age.

The rheumatic pains usually attending the disease are not always present, or they may be so slight as scarcely to attract attention. This has lead Jocheray<sup>24</sup> to distinguish two varieties of osteitis deformans; a painful and a painless form. Cases II and IV of this report may be grouped under the painless variety. It will be recalled that in Case II the symptoms referable to arteriosclerosis and myocardial degeneration caused the patient to seek medical aid, and that he did not complain of any pain in the extremities. So also Case IV suffered from little pain. The symptoms in this case were arteriosclerotic in origin.

Interesting in this connection is the suggestion of Elting<sup>1,c</sup> that the pains in the early stages of osteitis deformans may be due to distention of the periosteum, a view advanced by Durney in 1757, in explanation of the pains in the initial stages of rickets. According to this view, the painless variety of the disease is due to its slow development. The periosteum in this instance being only gradually distended.

#### PATHOLOGY.

The more recent pathological studies of osteitis deformans have added little to our knowledge of the pathogenesis of the disease as described by Paget and Butlin. Some of the most fundamental problems of its pathology are still contended. Paget and Butlin believed the process to be inflammatory in nature. They based their conclusion upon a study of the histological picture, which shows changes associated with enlargement and with excessive production of imperfectly developed structures, and with increased blood supply. Still<sup>25</sup> believes that the primary process is a rarifying osteitis; and Higbee and Ellis<sup>1,c</sup> from their careful pathological study state that resorption of bone appears to be the initial histologically recognized change. According to these writers, the reparative processes alone should be regarded as inflammatory in nature, which follow the resorption of bone, and which result in new bone formation.

However at variance writers may be regarding the initial step in the process, all who have studied the pathology of the osseous changes, describe a similar microscopic picture: essentially this consists of a resorption of bone associated with the excessive production of a poorly calcified bone designated as fibro-osteoid tissue.

Packard, Steele, and Kirkbride picture the process as follows:

A. "Absorption of the compact substance causing enlargement and confluence of the Haversian canals. B. Formation of new bone which runs diffusely through the affected and the adjacent

\* Ref. 1, p. 54.

† Ref. 22, p. 610.

healthy portions. This new bone remains uncalcified, and is in turn resorbed. C. The conversion of the medullary substance into a vascular connective tissue containing fat cells, giant cells, and leucocytes. In a small proportion of the reported cases cysts filled with gelatinous material and giant celled sarcomata occur in the medulla. D. As a consequence of these three processes, the ordinary relations of the compact substance and medulla are destroyed. The bones become exceedingly thickened and asymmetrical, but since the new bone tissue remains uncalcified, its elasticity permits of great deformity of the long bones from weight of the body, and fractures do not occur." \*

Von Recklinghausen,<sup>25</sup> in particular, has emphasized the regressive changes of the fibrous marrow into gelatinous cysts, and the progressive changes leading to the formation in the long bones of small, brown, red tumors of the nature of giant-cell sarcomata. These, he regards as characteristic of a disease closely allied to Paget's disease, to which he has given the name of tumor-forming osteitis deformans (*tumorbildenden ostitis deformans*). Von Recklinghausen considers this condition as distinct from Paget's osteitis deformans, but Sternberg<sup>26</sup> contends that the two diseases cannot be differentiated histologically; clinically a point in the differential diagnosis is the comparative rarity in Paget's osteitis deformans of spontaneous fractures which are almost pathognomonic of the type described by von Recklinghausen.

On the other hand, the occasional occurrence of cases of osteitis deformans with tumor growth would appear to bring into close relationship the two types just considered. Collective studies of the reported cases have shown, however, that this relationship has been too strongly emphasized. Although Paget reports that of eight cases traced to the end five died with cancer or sarcoma, this is not true of the large number of cases recorded since then. Gruner, Scrimger, and Foster<sup>27</sup> state in a recent study of a case of Paget's disease with multiple sarcoma formation, that up to 1902, only 14 of the recorded cases were associated with tumor formation. Of these, four were carcinoma, five sarcoma, and four either carcinoma or sarcoma. Since 1902, and hence in more than one-half of the reported cases, Higbee and Ellis found mention of only two benign tumors.

What has been said of the microscopic changes observed in the bones of osteitis deformans helps to make clear the varied picture which these present in gross. As already mentioned, the two most important factors concerned in the production of the deformity are a temporary softening and a hypertrophy, followed usually by a progressive induration of the newly formed bone, so that after a period of years it may become of ivory-like hardness. This newly formed bone is at first soft, porous, and vascular, so that it yields when exposed to strain; but soon the process of new bone formation gains on the process of resorption and the bones thicken.

The bones of the calvarium may become markedly thickened, often measuring as much as 1.5 to 3.75 cm. ( $\frac{1}{2}$  to  $1\frac{1}{2}$  inches) in the thickest portions. The shape of the long bones presents an appearance well described by Fitz:

"The surface is smooth or rough, nodular, or protuberant; the cortex thickened or thinned, spongy or eburnated; the cancel

lated structure sclerosed or coarsely trabeculated; the marrow spaces obliterated or transformed into cavities of various size. The central canal of the long bones is narrowed or dilated, even to disappearance, and the deformity of these bones is further increased by various degrees of abnormal curvature. There is no uniformity in the distribution of these alterations, and a single bone may give evidence of the decalcification, and absorption, the formation of osteoid tissue and its calcification, which are the processes concerned in the production of the gross changes."

#### ETIOLOGY.

Our ignorance of the causation of osteitis deformans is nearly as great to-day as when the famous English surgeon first drew attention to it. In spite of the many carefully examined cases with pathological reports and radiographic studies, opinion is still much divided as to the exact nature of the condition. Many theories have been advanced. Heredity, syphilis, arthritis, and gout, trophic disturbances and the internal secretions have all been considered as causes. Each has found ardent supporters.

Heredity has long been supposed by some to be a determining factor in the etiology of the disease. Paget, himself, was not inclined to this view. In 1889, after he had seen 23 cases, he states: "I have tried in vain to trace any inherited tendencies to the disease. I have not known it in two members of the same family. Many have had gouty ancestors, but I do not think more than any other equal number of persons in the same rank in life."\* Since Paget, a considerable number of instances occurring in more than one member of the family have appeared in literature. I have been able to find about a dozen cases in which the affection existed in one or more members of the same family. Pick<sup>28</sup> reports the disease in father and daughter; Oettinger and Lafont,<sup>29</sup> in father and two sons; Smith,<sup>30</sup> in father and son; Chaffard,<sup>31</sup> in mother and daughter; Berger,<sup>32</sup> and Higbee and Ellis,<sup>33</sup> in mother and son. It will be recalled that in Case III, of this report there was sufficient evidence for believing that the disease was present in the mother of the patient. Lunn,<sup>34</sup> and also Manwaring-White,<sup>35</sup> report the disease in two brothers,† Stahl,<sup>36</sup> in this country, and Parry,<sup>37</sup> in England, report the occurrence of the disease in two sisters, and Kilner,<sup>38</sup> in a brother and sister. The number of cases in which family tendencies existed is too small to justify any definite conclusions as to the part played by heredity in this condition.

Within recent years a number of French writers, notably among them Lannelongue<sup>39</sup> and Fournier<sup>40</sup> have advanced the view that osteitis deformans is a late manifestation of hereditary syphilis, a form of syphilis hereditaria tarda. It is interesting in this connection that Paget, himself, states definitely that the disease is "not associated with syphilis,"§ for he was neither able to obtain a history of syphilis in any

\* Ref. 20, p. 401.

† Cf. Ref. 31. Lannelongue.

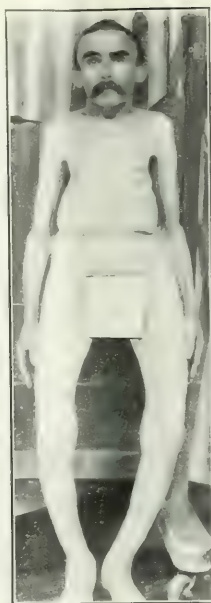
‡ Robinson (Trans. Path. Soc. Lond., 1887, XXXVIII, 262) reports the case of a clerk, æt. 52, whose brother about the same age suffered from the same disease.

§ Ref. 1, p. 55, 59.

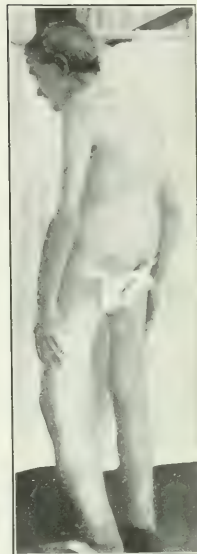
\* Ref. 5, p. 685.



CASE I.—Front view, showing general posture, broad pelvis, bowing of femora and of bones of forearm.



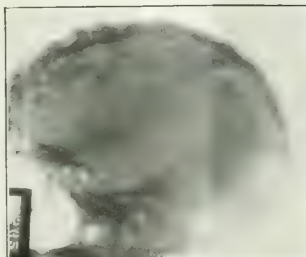
CASE IV.—View showing the simian attitude, the large head, flaring of ribs, transverse abdominal sulcus, and marked bowing of both femora and tibiae.



CASE II.—View showing low stooping, round shoulders, and position of head far forward.



CASE III.—Patient at 53 years of age. View showing posture, large head and disproportionate length of arms. Height: 5 feet 3 1/8 inches.



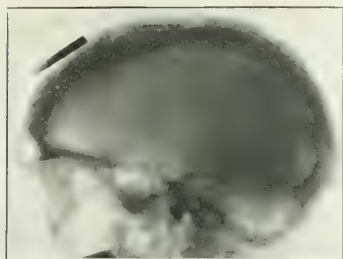
CASE III.—Skigram of skull showing thickening of inner and outer tables with a flocculent deposit of bone irregularly placed over the entire outer table. Sella turcica slightly enlarged.



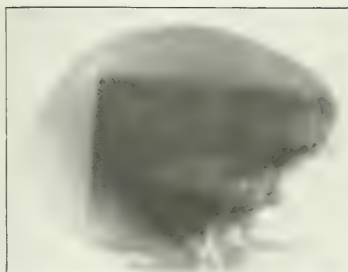
CASE III.—Patient at 28 years of age, showing erect posture. Height: 5 feet 7 to 8 inches.







CASE I.—Skull showing a uniform deposit of new bone. Total thickness about one inch.



CASE II. Skull showing a uniform and symmetrical thickening of the bones. Thickness one-half inch.



CASE II.—Skullgram of tibia and fibula; tibia irregularly thickened with longitudinal areas of porosis; fibula shows little calcification, but longitudinal areas of porosis. Marked sclerosis of posterior tibial vessels.



CASE III.—Skullgram of tibia and fibula showing thickening and small areas of porosis.





of the cases, nor could he demonstrate any known syphilitic changes in any of his patients.

The syphilitic nature of osteitis deformans is now largely discredited as a result of a more careful differentiation between the clinical and radiographic pictures of the two diseases. Clinically, the osteitis deformans of congenital syphilis may be differentiated from true Paget's disease by some of the points emphasized by Parkes Weber:<sup>38</sup> 1. The youthful age of the patients in the congenital syphilitic cases; 2, the relative absence of pain in those cases (here it is to be recalled that there is, according to Joncheray, a painless as well as a painful variety of osteitis deformans); 3, the favorable results obtained in the syphilitic cases under proper specific treatment; 4, in the syphilitic cases the tibiae are most severely and most frequently affected. In Paget's osteitis deformans the disease not rarely first shows itself in one of the femora; 5, in the syphilitic cases, in addition to the general enlargement, the affected bones often present irregular bosses on their surface; 6, there is no evidence of any tendency for malignant tumors to supervene in the bones of the syphilitic cases, as there is in the bones of Paget's class of cases; 7, in the former class of cases there may be present other obvious signs of congenital syphilis.\*

In 1902, Kienböck<sup>39</sup> showed by careful studies of radiograms of syphilitic bone affections and of Paget's disease that radiographically the two diseases could be differentiated. More recent comparative X-ray studies of the bones in osteitis deformans, hereditary syphilis, and osteomalacia by Legros and Leri<sup>40</sup> would seem to point in the same direction.

Another theory has for a time held sway and still finds adherents; viz., that which attributes the changes to trophic disturbances under the influence of the nervous system.† We know, for instance, that in certain diseases such as tabes, syringomyelia, and at times in diseases of the anterior horn cells, bony changes, often advanced, may be met with, and in a number of instances of Paget's disease diffuse alterations have been found in the spinal cord (two cases of Gilles de la Tourette and Marinesco,<sup>41</sup> and the case of Lévi<sup>42</sup>). But they have never been sufficiently definite or frequent enough to find a causal connection between them and the bony changes observed in Paget's disease.

Some writers, basing their views upon the experience of Schiff,<sup>43</sup> who was able to produce trophic changes in the bones of dogs (thickening of the tibia, fibula, and bones of the feet) by section of the sciatic and crural nerves, believed that the bony changes of Paget's disease are due to lesions of peripheral nerves. Schirmer‡ dismisses this view as carrying little weight, since in such experiments an atrophy of bones similar to senile atrophy is produced.

Furthermore, the theories which associate osteitis deformans with gout on the one hand, and arthritis deformans on the other, have little to support them. The gouty theory

is based largely upon the occurrence of so many cases of the disease in England, "the land of the gout," and upon the coincident presence of the disease in gouty individuals. According to Joncheray,<sup>44</sup> up to 1893, 40 of the 60 cases which showed this association were reported from England. As is pointed out by Higbee and Ellis,<sup>45</sup> however, England no longer has a preponderance of the cases. Of the 90 cases they collected from the years 1901 to 1911, only 13 occurred in England. Among the American cases very few were associated with gout.

Again, the view of Lancereaux,<sup>46</sup> and of Richard,<sup>47</sup> has met with little support. These writers regard osteitis deformans as part of the same morbid process which gives rise to arthritis deformans. Although it is possible to find some instances in which the two diseases have coexisted, there seems to be little reason for assuming any relationship between them.

Probably the most recent, interesting, and stimulating view is that which regards osteitis deformans as the result of a faulty metabolism, due to a perversion of the internal secretions. It is natural that the recent additions to our knowledge of the influence exerted by the hypophysis and the parathyroids in calcium metabolism should have called forth such views. The very recent work of MacCallum and Voegtlin<sup>48</sup> on tetany has especially emphasized the connection between the parathyroid secretion and the calcium exchange in the body.

Higbee and Ellis,<sup>45</sup> in their excellent communication on this disease present an interesting discussion of this view. These authors have been able to find only one reported case in which the hypophysis in osteitis deformans showed any definite change. This is the case of Bartlett,<sup>49</sup> who interprets the preponderance of large polygonal (chromophile cells) over the small cuboidal cells of the anterior lobe as a sign of increased functional activity of the gland. In the autopsy records of his second case, Stilling<sup>50</sup> described the hypophysis as soft, flabby, depressed and cyst-containing, and the posterior part of the sella and clivus as considerably raised; and Gruner, Scriver, and Foster<sup>51</sup> report an atrophy of the pituitary gland. In all the other recent reports in which this gland was studied, it is reported as normal. In only one of three of the cases of this report, in which skiagrams of the skull were obtained was the sella turcica larger than normal.

Whereas the thyroid gland was found sclerotic in three of the recorded cases (Lévi,<sup>42</sup> Hudelo and Heitz,<sup>52</sup> Higbee and Ellis<sup>45</sup>), little or no mention is made of the parathyroids. The association of osteitis deformans with an apparent absence of parathyroid glandules, which Higbee and Ellis report, would seem to be unique in literature. They found in the thyroid gland little islands of cells suggestive of parathyroid tissue. On the basis of this observation, they conjecture that an actual metaplasia of thyroid into parathyroid tissue may have occurred and that this parathyroid tissue was assuming the function of the absent or atrophied parathyroids.

Regarding the metabolism of osteitis deformans little is

\* Ref. 38, p. 86.

† Dr. Morton Prince, of Boston, strongly supports this theory (Tr. Ass. Am. Phys., 1902, xvii, 392.)

‡ Ref. 22, p. 694.

\* Pp. 374, 375.

Porter presents the results of a chemical analysis of portions of the diseased skull and tibia of his case, and of a healthy tibia in comparison with them. These analyses showed a reduction of the inorganic salts and phosphoric acid in the skull and tibia and the presence of fat which is absent in normal bone. The reduction in the magnesium salts was confirmed by Gilles de la Tourette and Marinesco and by Meyer, Langer and Gauckler.\* Higbee and Ellis state that the recorded urinary analyses show a varying output of calcium salts in this disease.

It would appear from these few observations that in the present state of our knowledge the assumption of a causal connection between the internal secretions and osteitis deformans is mere speculation; but as Higbee and Ellis point out, the metabolic processes in this disease are very little understood and it may be that accurate metabolic studies in osteitis deformans will help to solve the problem of its causation.

In conclusion, I desire to express my thanks to Dr. F. H. Bactjer for the interpretation of the X-ray plates, and to Dr. Louise Pearce for her assistance in photographing the patients.

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## DIABETES IN EARLY INFANCY.

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Diabetes mellitus is a disorder of nutrition, in which grape sugar accumulates in the blood, and is excreted over long periods in the urine even when only moderate amounts of carbo-hydrates have been ingested. This condition, always serious, is found most frequently in middle life. Thus in an elaborate tabulation based on French, English and German statistics, Lapine<sup>1</sup> found that 74 per cent of all cases occurred between 30 and 60 years of age, that but 2 per cent of the incidence of this disease took place between 1 and 10 years, and but 13 per cent before 30 years.

Among six thousand four hundred and ninety-six (6,496) fatal cases of diabetes occurring in England and Wales in ten years, 1861-1870, there were but eight under 1 year.

The condition would appear, therefore, to be among the rarest affections in early infancy.

This lends some interest to the following report of an instance of diabetes mellitus in an infant during its first year.

CASE A. P.—An infant girl, white, 9 months of age.

*Family History.*—Mother is well and a highly strung nervous woman. She had had an attack of rather severe jaundice two years before. The father, at present in good health, limps from healed tuberculosis of the hip. One sister aged four years is well. One brother died at four months, in the summer about two years ago, from gastro-intestinal disorder. There is no history of diabetes,

syphilis, or malignant disease in the family, and no other history of tuberculosis.

**Past History.**—The child's birth was normal; she was breast-fed with the addition of one or two bottles of diluted cow's milk for several months.

At four months she had a severe attack of bronchitis, during which the urine was found to contain pus cells, which, however, disappeared after the administration of urotropine. Several examinations of the urine, during the following months, showed it to be normal, containing no trace of sugar. At five months the child had some digestive disturbance and was put on malt soup mixture. She thrived for a time and gained rapidly in weight. She was first seen by the writer when she was about seven months of age; then she appeared to be perfectly well. Inquiry elicited the information that the child was receiving an unusually large amount of malt soup in her milk mixture, certainly over 10 per cent. This was discontinued and a simple milk mixture substituted, consisting of  $\frac{2}{3}$  milk,  $\frac{1}{3}$  water and 4 per cent dextrimaltose. The child did well for a month and then was seen on May 26, 1912, by my associate, Dr. M. L. Whittle, because she was not gaining in weight. At this time the physical examination was negative. The child was bright, but seemed rather irritable. The skin was dry and clear. Weight 19 $\frac{1}{4}$  lbs. There was no fever. Four days later, May 30, the child was found to have a temperature of 101° F. There was a definite "fruity" odor to the breath. She had lost 1 $\frac{1}{2}$  lbs. Examination of the urine showed it to contain between 4 per cent and 5 per cent of glucose. Acetone was present. There was no diacetic acid and but a trace of albumen.

The following day the child was put on *Eweiss* milk. Weight had fallen to 17 15/16 lbs. The temperature was 99.4° F. The sugar content of the urine diminished under this diet to 2 per cent and two or three days later to 1.5 per cent. The general condition of the child was not satisfactory and on June 7 she was admitted to The Johns Hopkins Hospital on the service of Dr. Barker, through whose courtesy I have the opportunity of reporting the case. Shortly after her admission the child apparently tired of *Eweiss* milk. The amount of acetone in the urine increased and the diet was changed to a mixture of 32 per cent cream, albumen and water, the mixture having a composition of about 3 per cent fat, 4 per cent sugar and 2 per cent proteid. On this the weight remained unchanged for several days. The condition of the urine is indicated in the following table:

June.....	8	9	10	11	12	13	14	15
Acetone.....	0	0	Trace.	Trace.	Trace.	Mod. Amt.	+	+
Diacetic acid..	0	0	0	0	0	0	+	+
Sp.gr.....	1018	1014	1016	1010	1013	1010	-	1008
Total urine..	290+	Not det.	160+	370	+	—	—	—
Sugar per cent.	.5	.4	.4	.4	.6	.8	1.0	1.4
Amount.....	1 gram	.7	.64	2.5	1.8	.12	....	....
				12 hrs.				

Each examination of the urine gave a strong, reddish precipitate with Fehling's solution, a black precipitate with Nylander's, a positive fermentation test and dextro rotation with the polariscope. Several examinations of the stools for sugar were negative.

A week after admission the patient became drowsy and refused nourishment. Increased amounts of acetone and diacetic acid were found in the urine. The cream mixture was changed to a whole-milk mixture to increase the amount of lactose and ward off the impending coma. A sodium bicarbonate 4 per cent solution was given by rectum and by gavage. There was no permanent improvement, the patient became more and more comatose, respirations were deep and sighing in character, and there was considerable nausea. The temperature rose and there was some evidence of pulmonary involvement. The urine throughout did not contain albumen or form elements.

The patient died eleven days after admission and after a recognized illness of about three weeks.

**Autopsy No. 3742.**—Performed four hours after death. Dr. Winternitz.

**Clinical Diagnosis:** Diabetes Mellitus.

**Anatomical Diagnosis:** Bronchopneumonia and cloudy swelling of viscera. Skin and mucous membranes pale. There were a number of scattered areas of bronchopneumonia in both lungs, more marked in the right.

**Heart:** Normal.

**Pancreas:** Was of normal size, somewhat triangular in shape, firm, of an ivory-gray color, and showed no excess of fibrous tissue on cross section. Lobules were homogeneous in appearance. Here and there very small spots were seen, apparently islands of Langerhans. The other viscera showed no macroscopical changes, except that the kidneys preserved their fetal lobulation. The cortex of each kidney was pale in contrast to the pyramidal portion which was much congested.

**Microscopical Examination.**—The thyroid showed some evidence of increased functional activity, in the misshapen acini and the high cubical cells lining them. A few of the alveoli were large, round and full of colloid.

Sections of the pancreas showed the lobules to be separated from each other by rather broad septa, which consisted principally of very loose connective tissue. There were many small round cells in the interstitial tissue, which in some places seemed to replace the acini. The connective tissue was increased. The islands of Langerhans were diminished in size and number. In one section none were seen. The capsule was thickened and in the connective tissue trabeculae were visible.

We have presented, therefore, a case of diabetes mellitus of probable pancreatic origin in an infant.

The points I should like to emphasize especially are the age of the patient, 9 months; the insidious onset, but rapid progress of the disease, three weeks of symptoms; the marked loss in weight, 2 pounds in 5 days; the absence of greatly increased thirst or hunger; the moderate polyuria; the early appearance of acidosis and coma and the negative findings at autopsy, except as concerned the slight but suggestive alterations in the pancreas.

I have attempted in the time at my disposal to collect the reported cases of diabetes *under one year* of age with the hope that some inferences can be drawn concerning this unusual but dangerous malady as it appears in early infancy. The number of cases in children *over* twelve months of age is of course considerably larger, as the incidence of the disease increases slowly with age until the third decade.

It seemed wise, however, to set an arbitrary age limit of one year to call attention to the occurrence of the malady in earliest infancy, when it is rarely suspected and often difficult to recognize, and because, too, diabetes in later childhood takes on the familiar features of the diabetes in adult life. (See table annexed.)

I am aware that the tabulation leaves much to be desired—that the urinary examination in the majority of instances is unsatisfactorily reported. The amount of urine in 24 hours is almost never given, doubtless partly because of the difficulty of obtaining it, and, of course, the more modern and selective tests for glucose were not applied in the examination of the early cases. Allowance being made for these unavoidable defects, a study of the clinical features and the results of treatment in the sixteen cases included in the table would suggest that they probably were cases of real diabetes, *i. e.*, that they exhibited a nutritional disturbance associated with



sugar (probably glucose) in the urine, persisting even when moderate amounts of carbo-hydrates have been ingested.

A second series of eleven cases, most of them reported as diabetes, but concerning the real nature of which there is much more uncertainty, have been omitted as "Doubtful Cases." In some the data were too fragmentary; others were probably cases of alimentary glycosuria. Concerning these no deductions can be drawn.

We are indebted for reference to some of the earlier cases to the collective investigation of Kulz<sup>2</sup> 1878, Stein<sup>3</sup> 1890, and of Wegeli<sup>4</sup> 1895. These writers have together reported upwards of three hundred diabetes cases in children under fifteen years of age. Of this number six have been included in our series as real diabetes during the first year and four others were classed as "doubtful."

*Incidence.*—The disease, although still, of course, very unusual in infancy, seems to be becoming more frequent. In more than forty years (1852 to 1896) but seven cases could be found reported, while the condition has been described in at least nine babies in the last fifteen years.

*Sex.*—Among adults it is well known that men are more frequently afflicted with diabetes than women in proportion of two to one or three to two, according to different investigators. This disproportion between the sexes does not seem to apply to diabetes occurring under 15 years, as the cases tabulated by Kulz, Stern, and Wegeli, above referred to, are about equally divided between boys and girls. In our series of 16 cases in early infancy the sex is given in 14 instances. Of these babies 11 were male and 3 female. Probably but little importance should be attached to this inequality between the sexes, as it is likely that a larger proportion of cases in girls was missed because of the difficulty of obtaining specimens of urine.

*Age.*—The babies in our series can be divided into two general classes, according to their age at the beginning of symptoms, namely, those in which the condition was noticed within a few days after birth (3 cases), and those in which several months elapsed, usually five or more, before the disease was recognized (13 cases). The cases are too few to admit of theorizing, but they suggest that the defect in the carbohydrate assimilation, though it be congenital, may not be more severe than when the disease begins a little later in infancy, for one infant (No. c), in which definite symptoms with glycosuria were discovered shortly after birth, recovered and another one (No. a) lived for at least eight months.

*Family History.*—In but half of the cases is there any statement as to the family history. In three instances it was good throughout; in three a grandparent or a great-aunt had had diabetes; in two there was an indefinite tuberculous family history. In one of the "doubtful" cases two older children in the family had the same condition as the 3-months-old baby, which was, however, almost certainly alimentary glycosuria.

*Causal Factors.*—In four instances there are no suggestions offered as to any possible cause for the condition.

Of the twelve remaining cases in six instances the condition seems to have followed an injury to the central nervous system.

In two of this group (Nos. b and g) the patients, aged 7 and 10 months, respectively, sustained a severe fall, striking the head; this was followed in one case by repeated convulsions and in the second by continued restlessness and a sharp rise in temperature. In two other instances belonging to this general group the symptoms may have been associated with injury at birth, as the labors were described as difficult, one (No. h) being a face presentation, the other (No. p) resulting in a head abrasion, which required six weeks to heal.

It would be interesting to follow the urine of a series of babies born after protracted and difficult labors to determine whether in them a larger proportion of transient glycosuria or diabetes mellitus develops than in the average baby.

The four remaining instances were associated either with increased cerebral pressure or deformity of the brain—hydrocephalus (Nos. d, k and m) and encephalus (No. n). It is not my purpose to discuss in this connection the neurogenous theory of diabetes or whether injury to or pressure upon the central nervous system can produce diabetes independently of the pancreas. As is well known, Von Noorden<sup>5</sup> holds that all these cases are either transitory non-diabetic glycosuria or true pancreatic glycosuria affected by nervous influences. In any case the appearance of persistent glycosuria following mental shock or injury to or disease of the brain or spinal cord is a well-recognized sequence and the proportion of these cases seems to increase inversely to the age of the patient. In one case (No. i), in which the onset was insidious and the conditions, although alarming for a time, ended in recovery, the author considers the disease to have been due either to irritation of the central nervous system, the result of painful dentition, or an arrested development of the pancreas. Neither of these explanations seems satisfactory. In three other cases, our own included, the beginning of the symptoms followed an unusual amount of sugar in the diet. One baby (No. f) was fed on condensed milk, another, that of Langstein (No. o), received 150 grams of sugar in addition to a liter of milk, that is, about 200 grams daily; and in my own case, as already pointed out, about a liter of milk was given, containing 10 per cent malt soup. A number of writers, including Griesinger, Cantani and Naunyn, are quoted by Langstein<sup>6</sup> as favoring this cause for certain cases of diabetes. It would appear a little suggestive that, in the case cited by Langstein and in my own, definite diabetes mellitus should arise in previously well babies 8 months of age, both of which had been given an unusually large daily amount of sugar.

*Symptoms.*—The majority of the cases of the series showed several symptoms in common. At first, restlessness was usually noted; this was followed by increased thirst and hunger and the passage of a larger amount of urine; loss of weight was a prominent symptom wherever the descriptions are adequate.

Multiple abscesses were present in two cases (Nos. b and f); gangrene of the lung in one (No. d); sore over the sacrum

\* See bibliography to table of cases.

No.	Observer.	Date.	Sex.	Age.	Family History.	Causal Factors.	Symptoms.	Urinary Findings.			Duration of Illness.	Result.	Diet and Treatment.	Autopsy Findings.		
								Sp. Gr.	Variety	Per Ct.						
a.	Kitselle.....	1852	M.	A few days.	?	?	Restlessness, thirst, hunger, constipation, polyuria, loss of weight; urine sweet like honey, napkins sticky. After 8 months urine offensive.	?	....	?	Large	8 months.	Died.	Breast milk, gem-mel tea, bread and water, Dovers powder.	.....	
b.	Rosbach.....	1871	F.	8 months.	?	Fall on head at 7 mos. Severe contusion of brain.	Repeated convulsions after fall, followed by unconsciousness, vomiting, sub-normal temperature, irregular respiration, cyanosis, thirst, polyuria, furunculosis, emaciation.	?	Glucose	2-10	Large	3 months.	Died.	Diluted milk and cream broth.	Left kidney slightly enlarged, brain and pancreas not examined, cloudy swelling.	
c.	Busch.....	1876	?	Under 1 year.	Unknown.	?	Restlessness, great thirst, emaciation, coma, ending in death.	1025	Glucose	5	?	23 days.	Died.	Nothing given.	.....	
d.	Hagenbach....	1879	M.	8 months.	Not stated.	Hydrocephalus.	Great thirst, marked polyuria. After 13 months gangrene of lungs.	1036	Glucose	+	?	Large	13 mos.	Died.	Milk diet, salicylic acid.	Gangrene of lungs, chronic hydrocephalus.
e.	Garnerus.....	1884	M.	A few days.	Good.	Congenital or possibly from chill following bath.	Restlessness, hunger, thirst, polyuria.	1010	Glucose	+	?	Large	2 months.	Recovery.	Milk with oatmeal water, buttermilk with 1 glycerine. On this the glycosuria disappeared.	.....
f.	Nichus.....	1891	M.	3 months.	Grandfather died of diabetes.	Fell on condensed milk.	Polyuria, abscesses.	....	?	2-3	Large	?	Died.	Condensed milk.	.....	
g.	Tavaria.....	1893	M.	10 months.	Parsi Indian.	Fell from cradle.	Shortly after fall, elevation of temperature, restlessness, thirst, dyspnea, flies attracted to napkins.	?	Glucose	+	?	Large	2 weeks.	Died.	Breast milk, diluted milk.	Pneumonia.
h.	Bell.....	1896	M.	3 months.	Father's aunt died of diabetes, and mother's grandfather of tuberculosis.	Difficult labor. Face presentation.	Restless, thirst, polyuria, fruity odor to breath, eczema, coma.	?	Glucose	+	?	Large	Several days.	Died.	Breast milk, skim milk diluted.	Nothing abnormal.
i.	Caillot.....	1900	F.	5 months.	Good.	Painful dentition.	Edema, restlessness, hunger, thirst, polyuria.	?	Glucose	1.51	Large	3 weeks.	Recovery.	Breast milk sugared, arrested development of pancreas.	.....	
k.	Orloff.....	1901	M.	5 months.	Not stated.	Hydrocephalus.	Restlessness, hunger, thirst, polyuria, loss of weight, sore on sacrum.	?	Glucose	+	?	Large	Several days.	Died.	Not stated.	Dilatation of lateral ventricle.
l.	Young.....	1901	M.	6 months.	Foundling.	?	Restlessness, indigestion, vomiting, dry skin, fever, polyuria.	1030	Glucose	5	Large	1 month.	Died.	Pasteurized milk mixture, 4% fat, 7% sugar, 2% proteid.	Both kidneys greatly enlarged, "parenchyma inflamed."	
m.	Langstein.....	1909	M.	6 months.	Not stated.	Chronic hydrocephalus.	Repeated convulsions. No intestinal disturbance.	?	Glucose	0.1-1	.....	A few months.	Died.	Not stated.	Internal hydrocephalus.	
n.	Langstein.....	1909	M.	7 days.	Not stated.	Anencephalus.	No intestinal disturbance.	?	Glucose	+	?	9 days.	Died.	Breast fed.	Complete lack of cerebral hemispheres.	
o.	Langstein.....	1909	M.	8 months.	Good.	Excess of sugar in diet 150 grams + 1 liter of milk.	Some intestinal disturbance, thirst, hunger, loss in weight, skin dry, acetone present.	?	Glucose	6-10	Large	Several months.	Apparently well.	Cows milk diluted, then casein and cream mixture, then oatmeal gruel plus small quantities casein cream mixture bouillon and green vegetables, sodium and bicarbonate.	.....	
p.	Eaton and Woods	1911	M.	6 months.	Mother's mother died of diabetes.	Labor instrumental and difficult; abrasion of head.	Two toes red and swollen, napkins sticky, thirst, polyuria, acetone present.	1035	Glucose	6-10	Large	2 years.	Died after 2 years.	Breast fed, washed cream mixture plus broth.	.....	
r.	Knox.....	1913	F.	8 months.	Father had tuberculosis of hip.	Excess of malt soup (almost 10%) + 1 liter of milk.	Loss of weight, skin dry, drowsiness, acetone, sighing respirations, coma, fever.	1010 to 1035	Glucose	0.5-1.5	Large	3 weeks.	Died.	Milk mixture plus dextrin maltose, Elweis milk cream albumin mixture.	Diminution in number and size of islands of Langerhans, broncho-pneumonia.	

in another (No. k). At least three cases ended in coma (Nos. c, h, and r). Acetone was noted in the breath or the urine in four instances (Nos. h, o, p, and r).

Thirteen cases died; three apparently recovered. The first two of these cases were definitely milder in type; the last, reported by Langstein, though not of the severest type, was probably helped by prompt and efficient therapy. Whether the condition will return or not is uncertain.

*The Duration of Illness.*—As may be expected, the length of time from the beginning of symptoms to their termination, either in sugar-free urine or in death, is very variable, depending largely upon the severity of the disease. The majority of the more rapid cases terminated in three weeks; one of them (No. h) in several days. Eaton's case lived for two years, and others survived several months.

*Urinary Findings.*—As has already been intimated, the urinary findings in the earlier cases are very incomplete; the diagnosis rests upon the finding of sugar, presumably glucose, which ferments with yeast and precipitates Fehling's solution, and upon the general symptomatology. In the last three cases glucose was definitely demonstrated in the urine by the phenylhydrazin test (Fisher).

The average specific gravity of the urine in the six cases which have been recorded is high for the urine of infants, being from 1010-1036. The amount in 24 hours was in every case large, but was only measured accurately in the case of Langstein (No. o), when in one 24-hour interval 680 cc. were passed. There is a record of the percentage of sugar in individual specimens in nine cases; it varied from 1 to 10 per cent. In nearly every instance the precipitate with Fehling's solution is described as abundant; albumen was practically never present in any considerable amount; and formed elements were not described. It is interesting that attention was drawn to the condition of the urine in several instances by the stiffness of the napkins after drying. In the Indian case (No. g) the collection of flies on the napkins first aroused suspicion. In an older child the white sugar remaining upon the floor, where the child had voided, suggested the nature of the malady.

It has, of course, long been known that the mere presence of glucose, even in considerable quantities, in the urine of infants does not establish the diagnosis of diabetes. As Grisz<sup>\*</sup> and many others have pointed out, reducing substances are frequently found in infants' urine, and in cases of gastrointestinal disorders, for example, lactose or a cleavage product of it is frequently present, even in the urine of breast-fed infants. The limit of assimilation for milk sugar is, in normal infants, about three grams per kilo of body weight, and this amount is greatly reduced in many intestinal disorders. In certain toxic conditions it is asserted by Helmholtz<sup>7</sup> that one-hundredth of the amount of lactose assimilated by a normal child may produce lactosuria.

Aschenheim<sup>8</sup> has shown that the tolerance to grape sugar also varies greatly in certain other conditions. For example, in eczema the tolerance may fall to .75 of a gram per kilo body weight, and he considers that from 80 to 85 per cent of

eczematous infants have glycosuria when taking the normal diet. Cobliner<sup>9</sup> has recently pointed out that the percentage of sugar in the blood of infants averages 0.119 per cent, a considerably higher content than that of adult blood, which contains, according to Leifmann and Stern,<sup>10</sup> about 0.085 per cent. Children with exudative diathesis have hyperglycæmia, associated, as we have seen, with a lowered tolerance; while in the decomposition or atrophy there is hypoglycæmia. It is, therefore, necessary in making a diagnosis of diabetes in infancy to consider both the condition of the patient, the diet, the probable carbo-hydrate tolerance and the amount of sugar in the urine when the patient is taking a carbo-hydrate free diet.

*Diet and Treatment.*—But little can be learned from the consideration of the diet and treatment of the early cases; most of them received milk in some form; several of them breast milk. In one case (No. b) the glycosuria was reduced by diluting the milk mixture and adding cream. In another (No. e) a diet of butter milk and the administration of salicylic acid in large doses is said to have decreased the urine and the sugar output. In the last three cases of the series, those of Langstein, Eaton and my own, a definite effort was made to reduce the sugar of the milk mixture. Langstein's case is particularly instructive. His patient, 8 months of age, was given a milk mixture, two parts of milk, one part of water, about 1300 grams in 24 hours, divided into 5 feedings. This diet contained about 40 grams of sugar. There was excreted in the urine at this time from 6 to 8 per cent of glucose, the kind of sugar being accurately determined. No acetone nor diacetic acid was present. The attempt was made to render the urine sugar free by feeding the small patient a milk mixture from which the lactose was to a large extent removed. It was prepared as follows:

The casein of a liter and a half of milk precipitated by rennin was collected in a cloth and thoroughly washed. It was then passed through a fine sieve into a mixture of 200 grams of cream and 1300 grams of water and sweetened with saccharine. On this diet the sugar content of the urine fell to about 8 grams a day, approximately the quantity furnished in the mixture. Under these conditions, however, acidosis quickly developed, the ammonia co-efficient increased 33 per cent, corresponding to a quantity of about 1.4 per cent of ammonia excreted.

The child became somnolent, apathetic and without appetite. Five grams of sodium bicarbonate were given daily without producing much change in the condition. At this time a liter of thick oatmeal gruel was introduced by a stomach tube in five feedings on each of two succeeding days. This was followed by a marked improvement in the patient's symptoms. The urine became sugar-free and the acetone bodies quickly disappeared. A small quantity of milk mixture was now carefully added as follows:

The curd from a liter of milk and 100 grams of cream were suspended in 900 grams of oatmeal gruel and given in 24 hours. The quantity of cream was gradually increased; when it reached 300 grams sugar again appeared in the urine, 4 to



5 per cent in 600 or 700 cc. of urine. Again an oatmeal gruel day was substituted and in addition a little bouillon and a green vegetable were added to the modified milk mixture. In this way the sugar tolerance of the infant was increased until it could take 16 grams of milk sugar in addition to the carbo-hydrate gruel without any glycosuria or acidosis; an increase of the sugar intake beyond this point was always followed by glycosuria. On this diet there was no loss in body weight and at the close of the report the child was doing well, although its ultimate recovery is of course uncertain.

I have gone into the details of this case because it is unique in the literature and also for the reason that it shows well how the dietetic measures which have been more or less successful for many years in combating the progress of diabetes in adults can be made applicable in the treatment of the same condition in infants. The remarkable results following the so-called oatmeal cure are not at present thoroughly understood. It has been shown, however, by Czerny and Keller that the milk sugar is better assimilated when it is given together with the second carbo-hydrate in the form of a cereal mixture, but this fact does not explain the greatly increased value of oatmeal gruel as compared to other cereals.

In Eaton's case an improvement was noticed after the administration of washed cream in addition to the breast milk; this was prepared by taking the cream off a quart of milk, shaking it with an equal quantity of water, and, after the cream had again risen, making a mixture of one part cream to four parts water; to this a little saccharine was added. An analysis of the mixture is not given, but it contained, of course, comparatively little lactose. The child was given 51 oz. of the mixture several times a day. Although the sugar in the urine of this child was unquestionably grape sugar, and acetone and diacetic acid were frequently present, there was no suggestion of coma and the case was evidently one of comparatively light severity.

In our own case, when the glycosuria was discovered an attempt was made to reduce the carbo-hydrate of the food by the use of *Eiweiss* milk, having a sugar content of about 2 per cent. This was successful for a few days only, when the child became somnolent and the acetone bodies increased markedly in the urine; notwithstanding the exhibition of large quantities of sodium bicarbonate and an increased amount of carbo-hydrate, the case went on to a rapidly fatal coma.

**Autopsy Findings.**—Partial post mortem examinations were made in nine instances and add little to our knowledge.

Hydrocephalus was described in three cases and a gross defect in cerebral substance in a fourth, as had been noted during life. In our case alone was there any microscopical examination of the pancreas. In this, as above described, there was apparently a reduction in number and size of the islands of Langerhans. The importance of this finding is emphasized by Heiberg.<sup>11</sup>

**Summary.**—It has been the purpose of this paper, in connection with the report of an instance of diabetes mellitus in early infancy, to present briefly other cases of the same disease occurring during the first year. The urinary findings are

usually incomplete, but a consideration of all the symptoms given warrants the probable diagnosis of diabetes mellitus in the cases of 15 additional babies under one year reported from 1852 to the present. The majority of these cases were males.

Heredity seems to have played but little part.

Continuous over-feeding of sugar preceded the onset in three cases.

Injury to or alteration of the central nervous system was often associated with the beginning of the malady.

The more common symptoms were increased thirst and hunger, loss of weight, polyuria, and glycosuria; acidosis and coma occasionally ended the scene.

The prognosis is grave, but not hopeless, even in infancy, except in a severe grade of the disease.

Treatment should be begun early, and, although more difficult in carrying out, should follow the lines found most successful in the treatment of diabetes in adults, *i. e.*, the patient's carbo-hydrate tolerance should be determined and the sugar content of the diet (milk mixture) correspondingly reduced, the calorific requirements being furnished by fats and proteids.

An "oatmeal day" or days should be given at frequent intervals.

Diabetes mellitus is fortunately a rare affection of early infancy, but undoubtedly cases pass unrecognized, as do other conditions in babies, because of the failure to examine the urine of these patients systematically.

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# THE PRODUCTION OF PASSIVE HYPERSENSITIVENESS TO TUBERCULIN.<sup>1</sup>

## SECOND PAPER.

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AND

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*Laboratory Assistant.*

About fifteen months ago I spoke before this society on the production of passive hypersensitiveness to a tuberculo-protein; a protein since shown by work in the laboratory of the Phipps Dispensary<sup>1</sup> to be identical with the sensitizing fraction of tuberculin. In this report<sup>2</sup> the results of previous attempts passively to sensitize animals to tuberculin with the serum of tuberculous human hosts were detailed. The negative findings of Friedmann,<sup>3</sup> Eitner and Stoerk,<sup>4</sup> Roepke and Busch,<sup>5</sup> Novotny,<sup>6</sup> Onaka,<sup>7</sup> Simon,<sup>8</sup> Romer and Joseph,<sup>9</sup> Joseph,<sup>10</sup> Frankel,<sup>11</sup> Kraus, Lowenstein and Volk,<sup>12</sup> of Kraus<sup>13</sup> and others were mentioned. The results of Yamanouchi<sup>14</sup> and the evidence furnished by A. K. Krause<sup>15</sup> discrediting them were outlined, and the doubtful character of the findings of Bauer,<sup>16</sup> of Helmholtz<sup>17</sup> and of Bail<sup>18</sup> were indicated. The observations of Bruck<sup>19</sup> alone seemed to show a measure of success in the attempts passively to sensitize normal guinea pigs with the serum of tuberculous individuals. In this preliminary report, too, the results of experiments on passive hypersensitiveness to tuberculin made in the research laboratory of the Phipps Dispensary for Tuberculosis were described and the following conclusions were drawn:

1. Tuberculin hypersensitiveness in man is a condition of true anaphylaxis and that in cases of tuberculin idiosyncrasy at least sensibilisin may be present in the circulating blood; and

2. The failure of previous work may perhaps be explained on the theory that in most instances of tuberculin hypersensitiveness sensibilisin is to be found only in the tissues of the body, and either not at all, or only in minimal amounts in the circulation; whereas, in the rare cases in which a maximal grade of sensitiveness to tuberculin exists, there is sufficient circulating antibody passively to sensitize animals injected with their blood.

The work reported in this preliminary communication has been confirmed by Thiele and Embleton.<sup>20</sup>

The following experiments were made in order to determine if the blood or serum of tuberculous individuals, with an average degree of hypersensitiveness to tuberculin, will sensitize normal guinea pigs.

### EXPERIMENTAL PART.

Thirty-five patients, all infected with the tubercle bacillus, and all showing positive von Pirquet and Calmette reactions,

<sup>1</sup>Read at a meeting of the Lænnec, a society for the study of tuberculosis, The Johns Hopkins Hospital, Apr. 28, 1913.

were studied. The technic employed was in brief as follows: Fifteen cubic centimeters of blood were obtained from each patient by vena puncture and the coagulation of the blood so drawn was inhibited by the addition of 1.5 per cent sodium citrate solution. Normal untreated guinea pigs, 250-300 grams in weight, were each injected with the equivalent of five cubic centimeters of whole blood.

Serum was used in only four experiments, inasmuch as our earlier work had clearly demonstrated that the blood is a more efficient sensitizer than is the serum. The sensitizing injections were made into the peritoneal cavities, and 20-48 hours later the guinea pigs were tested by an intracardiac injection of a solution containing 0.009-0.015 grams of tuberculo-protein prepared according to the technic of Baldwin.<sup>20</sup> There is no need to detail the experiments made. Briefly, it may be stated that definite positive results were obtained with the blood of only one of the patients examined.

This individual was a white man aged 32 years. He showed the signs of a moderately advanced bilateral pulmonary tuberculosis and was extremely sensitive to tuberculin. The installation of one drop of a 1 per cent solution of old tuberculin into the left conjunctival sac caused the development not only of conjunctival hyperemia, but purulent secretion, chemosis and photophobia as well. Likewise the response to the von Pirquet skin test was very marked. The blood of this patient led in five of the six animals injected with it to the development of so sensitive a state that the reinjection of the animals with tuberculo-protein 40 hours later caused acute death. Four of the five animals that succumbed developed the typical symptoms of acute anaphylactic shock and post mortem showed the massive pulmonary emphysema, subepicardial hemorrhages and delayed coagulation time of the blood, so characteristic of true anaphylaxis. The fifth animal showed in addition to these signs a small hemorrhage into the pericardial sac, an accident which obscures the interpretation of the result.

It is interesting that negative results were obtained when the blood of five patients who had been treated with large doses of tuberculin was used as the sensitizing agent. This, in spite of the fact that the blood was drawn three to eight weeks after the cessation of specific therapy, at a time when *a priori* it might have been expected that active hypersensitiveness had developed, not only as a consequence of the disease,

but from the injection of so large a quantity of foreign protein.

These experiments seem to us completely to establish the conclusions of our preliminary report already stated, and to show that free circulating sensibilisin is not present in most cases of pulmonary tuberculosis.

A valid criticism of the last statement is pertinent. The

prepare anaphylotoxin according to the method of Friedberger. This procedure was adopted because it had been shown by Sata<sup>21</sup> that "it is possible through a simple mixing in vitro of old tuberculin or powdered tubercle bacilli with the serum of immune animals, under optimum conditions, to produce a toxin which can elicit a recognized tuberculin reaction or typical anaphylactic death in normal guinea pigs."

TABLE I (GRAY—HETROTH).

Preparation.	Incubation.		Weight of Guinea Pig.	Injection.	Symptoms.	Autopsy.
	Time.	Temperature.				
1.0 cc. Blood + 1.0 cc. O. T.	24 hours.	37° C.	275 grams.	Intravenous 1.5 cc.	Restless.	No characteristic lesions.
1.0 " " + 0.5 " " "	" "	" "	280 " "	" " "	" " "	" " "
1.0 " " + 0.3 " " "	" "	" "	290 " "	" " "	" " "	" " "
1.0 " " + 0.25 " " "	" "	" "	274 " "	" " "	None.	" " "
1.0 " " + 0.2 " " "	" "	" "	258 " "	" " "	" " "	" " "
1.0 " " + 0.15 " " "	" "	" "	260 " "	" " "	" " "	" " "
1.0 " " + 0.1 " " "	" "	" "	265 " "	" " "	" " "	" " "
1.0 " " + 1.0 " Protein	" "	" "	272 " "	" " "	Restless.	" " "
1.0 " " + 0.5 " " "	" "	" "	275 " "	" " "	Sneezing.	" " "
1.0 " " + 0.5 " " "	" "	" "	275 " "	Intracardiac	None.	" " "
1.0 " " + 0.4 " " "	" "	" "	340 " "	" " "	" " "	" " "
1.0 " " + 0.3 " " "	" "	" "	263 " "	" " "	" " "	" " "
1.0 " " + 0.2 " " "	" "	" "	250 " "	" " "	" " "	" " "
1.0 " " + 0.1 " " "	" "	" "	275 " "	" " "	Death in 1 hour.	Haemorrhage into pericardial sac.
1.0 " " + 1.0 " Pulv. B.	" "	" "	274 " "	" " "	None.	No characteristic lesions.
1.0 " " + 0.5 " " "	" "	" "	274 " "	" " "	Death in 6 hours.	Haemorrhage into pericardial sac.
1.0 " " + 0.5 " " "	" "	" "	269 " "	" " "	None.	No characteristic lesions.
1.0 " " + 0.2 " " "	" "	" "	280 " "	" " "	Immediate death.	Haemorrhage into pericardial sac.
1.0 " " + 0.2 " " "	" "	" "	275 " "	Intravenous	None.	No characteristic lesions.
1.0 " " + 0.15 " " "	" "	" "	294 " "	" " "	" " "	" " "
1.0 " " + 0.10 " " "	" "	" "	260 " "	" " "	" " "	" " "

Same scheme carried out with blood of other patients, using varying incubation periods up to 216 hours.

TABLE II (SCHAEFFER).

Preparation.	Incubation.		Weight of Guinea Pig.	Injection.	Symptoms.	Autopsy.
	Time.	Temperature.				
1.0 cc. Blood + 0.5 cc. Pulv. B. + 0.5 cc. C.	Immed. injec.		250 grams.	Intracardiac 1.5 cc.	Restless. Dyspneic.	No characteristic lesions.
1.0 " " + 0.5 " " "	1 hour.	37° C.	250 " "	" " 2.0 "	" " "	" " "
1.0 " " + 0.5 " " "	2 hours.	" "	275 " "	" " 2.0 "	Sneezing. Fall of 3° C. in temp.	Haemorrhage into pericardial sac.
1.0 " " + 0.5 " " "	" "	" "	264 " "	" " 1.5 "	No symptoms.	No characteristic lesions.
1.0 " " + 0.5 " " "	" "	" "	255 " "	" " 1.75 "	" " "	" " "
1.0 " " + 0.5 " " "	" "	" "	270 " "	" " 1.75 "	" " "	" " "
1.0 " " + 0.5 " " "	" "	" "	265 " "	" " 1.75 "	" " "	" " "
1.0 " " + 0.5 " " "	120 "	" "	280 " "	Postorbital 1.5 "	Immediate death.	Pontile haemorrhage.
1.0 " " + 0.5 " " "	148 "	" "	270 " "	" " 1.5 "	Sneezing. Dyspneic.	No characteristic lesions.
1.0 " " + 0.5 " " "	190 "	" "	270 " "	" " 1.5 "	No symptoms.	" " "
1.0 " " + 0.5 " " "	216 "	" "	265 " "	" " 2.0 "	" " "	" " "
1.0 " " + 0.5 " " "	48 "	11 "	255 " "	Intravenous 1.5 "	" " "	" " "
1.0 " " + 0.5 " " "	96 "	11 "	255 " "	" " 2.0 "	" " "	" " "
1.0 " " + 0.5 " " "	180 "	" "	263 " "	" " 1.75 "	" " "	" " "
1.0 " " + 0.5 " " "	200 "	11 "	280 " "	" " 1.5 "	" " "	" " "

Same scheme carried out, using varying proportions of blood and different antigens.

TABLE III (WEINBERG).

Preparation.	Incubation.		Weight of Guinea Pig.	Injection.	Symptoms.	Autopsy.
	Time.	Temperature.				
3.0 cc. Blood + 0.33 cc. Protein + 0.5 cc. C <sup>1</sup>	24 hours.	37° C.	270 grams.	Intracardiac 1.5 cc.	No symptoms.	No characteristic lesions.
2.0 " " + 2.0 " " "	" "	" "	253 " "	" " 1.5 "	" " "	" " "
3.0 " " + 0.33 " O. T.	" "	" "	260 " "	" " 2.0 "	" " "	" " "
2.0 " " + 2.0 " " "	" "	" "	260 " "	" " 1.5 "	Restless. Dyspneic.	" " "
2.0 " " + 2.0 " A. F.	" "	" "	265 " "	" " 1.5 "	Prompt death.	Haemorrhage into pericardial sac.
2.0 " " + 2.0 " " "	" "	" "	271 " "	" " 1.5 "	No symptoms.	No characteristic lesions.

Blood-protein mixture used in primary injections incubated up to 148 hours—negative results.

O. T. = Old tuberculin. A. F. = Albumose-free tuberculin. Pulv. = Powdered tubercle bacilli. C<sup>1</sup> = Complement (guinea-pig's serum 1-10). Protein = Protein obtained by aqueous extraction of tubercle bacilli.

method used may not have been sufficiently refined to detect minimal amounts of the specific sensitizing substance. It may be that the blood is so diluted after injection into an animal as to provide too little of the active sensitizing agent, or that at the time it contained too little anti-substance passively to sensitize normal animals.

To overcome these objections, the blood of tuberculous patients was incubated with tuberculo-protein, with various tuberculins, or with pulverized tubercle bacilli in order to

The details of the technical procedures will not be considered here. The serum and the citrated blood of the tuberculous hosts were incubated for varying periods of time (3-16 hours) and at different temperatures (6 to 40 degrees centigrade), with old tuberculin, albumose-free tuberculin, pulverized tubercle bacilli and so-called tuberculo-protein, in proportions that varied from one to one to nine to one. At the end of the incubation period the serum or the blood protein mixtures were centrifugalized and the supernatant fluid



was injected into normal guinea pigs. The test solutions were introduced into the heart, the jugular vein or the subdural space of the animals. Not only were manifest symptoms of hypersensitiveness watched for, but variations of temperature were noted. The tables clearly illustrate the procedures employed in some of the many experiments made.

For the sake of brevity suffice it to state that though the blood and the serum of patients were tested by this method; that though many combinations of varying quantities of blood or serum with complement and antigen, and variations of the duration and the temperature of incubation were tried, no definite positive results were obtained. Some of the animals tested did develop symptoms, but the nature of them was equivocal; some of them did show marked variations in temperature, sudden rises or falls, but in no instance did acute lethal shock develop.

These results confirm the established fact that free sensibilisin, at least with the methods employed, is not to be demonstrated in the circulation of most individuals with pulmonary tuberculosis. However, the positive findings recorded in our preliminary paper and in the experiments just described, though exceptional, are important as evidence in establishing the anaphylactic nature of the tuberculin reaction.

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## SOME STRIKING EXAMPLES OF SUBNORMAL ACCOMMODATIVE POWER.<sup>1</sup>

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Twenty-two years ago, in a paper read before this society, and published in the Transactions for 1891,<sup>1</sup> I first described the condition for which the name "subnormal accommodative power" was suggested—a condition which I then believed to be, and now, with more extended experience, know to be, "a not infrequent cause of asthenopia in young persons." Three years later, in a shorter communication to this society,<sup>2</sup> I reported several typical cases of this condition, and mentioned, as bearing upon the relative frequency of its occurrence, that in 1615 consecutive cases of refractive and muscular anomalies met with in private practice which I had then recently tabulated the presence of subnormal accommodative power, more or less marked, was noted 155 times—about 9.50 per cent of the whole number of cases. More recently I have gone over the notes of 200 cases, many of them being those of persons beyond the presbyopic age, in whom the condition can seldom be recognized; included under the letters A and B in a later series of refractive and muscular faults, and found 22 cases of subnormal accommodative power—a little over 10 per cent of the total.

As my views regarding the nature of this anomaly and the means of detecting and dealing with it were fully set forth in the first paper upon the subject, to which I have referred, and more recently in my treatise upon "Prevalent Diseases of the Eye," I shall not lengthen this communication by repeating much that has already been said, but will content myself with the statement that the doctrine of subnormal accommodative power is based upon the observation that, while the normal balance of the lateral muscles of the eyes in distant vision, as shown by the vertical diplopia test, is one of orthophoria, in near vision (at the usual reading distance), the normal condition, as shown by the same test, is one of exophoria, there being usually a relative divergence of 3° to 4°. In other words, with induced vertical diplopia, exophoria of moderate degree at the reading distance is the real orthophoric condition, while "orthophoria," using the term as it is commonly employed, when present in near vision (with vertical diplopia) is a departure from the normal, and is to be regarded as truly a heterophoric condition. Expressed in another form, the vertical diplopia test at the reading distance should show, as compared with the result at 20', a difference in the sense of exophoria of 3° to 4°. When this is not the case subnormal accommodative power exists, and if the difference is 0° or but 1° it must be taken into account in the

<sup>1</sup> A paper read before the American Ophthalmological Society, Washington, May 7, 1913.

<sup>2</sup> Vol. VI, p. 127.

<sup>3</sup> Vol. VII, p. 138.

adjustment of glasses, if the patient is to obtain comfortable near vision.

In this connection it may be of interest to mention the case of Mr. F. W. Weymouth, a graduate of Leland Stanford University, who during the past winter has been engaged in post-graduate work, under Prof. W. H. Howell, in the physiological laboratory of The Johns Hopkins University, has recently made a study of the muscle balance, the range of accommodation, etc., of the eyes of 40 students in The Johns Hopkins Medical School. His carefully-conducted measurements showed for the whole number of eyes tested an average esophoria, in distant vision, of a small fraction of a prism-diopter, whereas in near vision, at 32 cm., he found an average esophoria of 5.02 prism-diopters, a difference, in striking confirmation of the view commonly held by ophthalmologists, of slightly more than 5 prism-diopters.

A goodly number of my ophthalmological confrères have been sufficiently impressed by the views I have advanced regarding the significance of subnormal accommodative power to put them into practice, and from some of them I have received gratifying reports as to the satisfactory results which they have obtained from doing so; but, judging from my clinical experience, a considerably larger number, it would seem, have not been so impressed; and, taking a narrow view of the matter, perhaps I should not complain of this, since it has afforded me not a few opportunities to relieve troublesome cases of asthenopia, when their efforts have been without avail.

I might cite a large number of cases in which the prescribing of glasses for subnormal accommodative power has proved most helpful; but it has seemed to me that a brief description of a few typical and striking examples of this anomaly would be more to the purpose.

CASE I.—Mr. H., æt. 42, engaged in newspaper editorial work in Philadelphia, and, therefore, compelled to use his eyes a great deal, especially at night, consulted me in January of this year. His asthenopic symptoms were very pronounced and he feared he would have to abandon his profession. He had not long before consulted an eminent ophthalmologist in his own city, who had given him glasses for near vision which corrected a low degree of astigmatism, and slightly over-corrected his manifest hypermetropia, from which, however, he derived but little relief.

With lenses which fully corrected his manifest fault and gave him  $\frac{20}{XV}$  vision, I found his muscle balance at 20', by the vertical diplopia test, varied from slight exophoria to orthophoria; but, when the test was repeated at the reading distance, 13", marked esophoria was revealed, which, even with the addition of +.62s to the distance correction, amounted to  $4\frac{1}{2}^\circ$ . When + 1.37s, instead of +.62s, was added to the distance lenses his near muscle balance varied from "orthophoria" (so-called) to esophoria of  $\frac{1}{2}^\circ$ , and, in reading, he willingly accepted, in addition,  $3^\circ$  of esophoric correction.

For distant vision lenses were prescribed as follows:

L. eye +.37s = +.37c 130°.

R. eye +.75s = -.50c 95°.

And for near vision:

L. eye + 1.75s = +.37c 130° = prism  $1\frac{1}{2}^\circ$  base out.

R. eye + 2.12s = -.50c 95° = prism  $1\frac{1}{2}^\circ$  base out.

Although he has not worn the distance lenses systematically, as advised, his asthenopia has been completely relieved by the near glasses, and up to the present time he has been able to continue his editorial work with comfort.

It would be difficult to find a more typical example of subnormal accommodative power than is afforded by this case, or a better illustration of the benefit which results from its recognition and correction. Probably because of congenital insufficiency of the ciliary muscles, an inordinate accommodative effort was required to maintain distinct near vision; but, because of the close relation between the accommodative and convergence centers, a strong stimulation of the ciliary muscles was necessarily accompanied by a corresponding stimulation of the internal recti; hence the esophoria, present only in near vision, and hence also the asthenopia, which commonly manifests itself, as is generally recognized, when the normal parallelism between convergence and accommodation is radically disturbed. The glasses prescribed, which afforded a considerably greater measure of help to the ciliary muscles than the refractive fault or the age of the patient called for, while at the same time they appreciably lessened the tension upon the hard-pressed external recti, relieved the asthenopia by restoring this normal parallelism.

It is interesting to note that two children of this patient, aged, respectively, 9 and 7 years, exhibit, to a less degree, the same fault as the father, for which both are wearing glasses.

CASE II.—Mr. A., æt. 26, a medical student in Johns Hopkins University, although his hypermetropic astigmatism had been accurately corrected by a confrère, still complained of asthenopia in near vision. In explanation of this he was found to have well-marked subnormal accommodative power. The glasses finally decided upon for distance were:

L. eye +.62c 160°.

R. eye +.50c 15°.

With these he had, for the two eyes,  $\frac{20}{XV}$  + vision, and at 20' an esophoria of  $1^\circ$ , but at 12" an esophoria of  $3\frac{1}{2}^\circ$  was found. The addition of + 1s to the distance correction sufficed only to eliminate this esophoria, and, theoretically, he should have had a stronger spherical lens than this, or some esophoric prismatic help, for near vision. It was decided, however, to try the effect of adding + 1s to the distance lenses, and this proved entirely successful; and to the present time he has been using these glasses in near vision and doing much hard work with his eyes without discomfort.

CASE III.—Mr. B., æt. 23, a student in The Johns Hopkins Medical School, with decided asthenopia and occasional diplopia in near vision, had consulted a well-known oculist in Washington, who prescribed for near vision:

L. eye —.25c 180°.

R. eye —.12s = —.50c 170°

As these failed to relieve the asthenopia, he subsequently came to me. Upon testing his muscle balance he was found to have, with these glasses, an esophoria at the reading distance of  $5^\circ$ ; without glasses, an esophoria at 20' of  $1^\circ$ , scant, was found — definite proof of subnormal accommodative power. He was given for near use:

L. eye +.87s.

R. eye +.50s = +.37c 75°.

With these he showed an exophoria at 12" which varied from 1° to 0°. His asthenopia promptly disappeared. Some months later there was a return of the symptoms, when a change in the astigmatic correction, but not in the spherical, was found to be necessary.

CASE IV.—Miss D., et. 19, was asthenopic and suffered with severe headaches. She was found to have a low degree of compound myopic astigmatism, complicated by pronounced subnormal accommodative power. For distance, glasses were ordered as follows:

L. eye —.37s = —.25c 50°.

R. eye —.12s = —.25c 90°.

With these she had  $V = \frac{20}{XV}$  — and orthophoria at 20'; but at 12" an esophoria varying in degree, at times amounting to 6°, was revealed. With +1.25s added to the distance correction there was still no exophoria at the reading distance. For near vision,

L. eye +.37s = —.25c 50° = prism 1° base out

R. eye +1.12s = —.25c 90° = prism 1° base out

were prescribed, and as she was not heard from again it is fair to presume that they afforded the desired relief.

It may be mentioned, as of interest, that this patient had been in the habit of holding a book, in reading, very close to the eyes, as though she were highly myopic, a circumstance not very unusual in high degrees of subnormal accommodative power. The explanation of this paradox evidently is that the individual finds the greater accommodative effort required in doing this more than offset by the greater compensating convergence which attends it. When the proper convex glasses are given the habit promptly disappears and the book is held at a normal distance.

It seems unnecessary to lengthen this paper with further reports of cases, for those which I have briefly described suffice to make clear the significance of the anomaly, the tests depended upon to reveal its existence, the annoying asthenopic symptoms to which it gives rise, the measures demanded for its correction, and the immense relief which these measures invariably afford; and this was all I had in view in bringing the subject once more to the attention of the members of the Ophthalmological Society.

## UNILATERAL SCLEROSIS OF THE PULMONARY ARTERY.

By FRANK A. EVANS.

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These studies were undertaken upon the presentation of a particularly interesting case, which showed an advanced unilateral sclerosis of the pulmonary artery associated with a condition of collapse and fibrosis of the opposite lung. This remarkable association, with such a striking difference in the character of the vessels of the two lungs, offered an excellent opportunity to investigate the pathological process which had occurred in the arteries and to associate these changes with the altered conditions in the pulmonary circulation.

It is rather infrequent in the human subject to have an opportunity of studying semi-experimental circulatory disturbances having pathological changes in the arteries as their sequel. Here, however, in a paired organ there was demonstrated a process by which the circulation had been profoundly altered in the one and which had secondarily led to circulatory changes (it may be increased pressure) in the arterial tree of its fellow organ.

The presence of small isolated nodules upon the surface of the pulmonary arteries has been repeatedly commented upon and these lesions are not uncommonly found, when properly searched for, in individuals above middle age. These nodular elevations, which present a yellow appearance, are seen at the points of bifurcation of the pulmonary arteries, as well as along the main stem. There appears to be no difference in their distribution in the two lungs, nor does it appear that any one lobe is affected more than another. These small plaques in the pulmonary vessels seem to bear no relation to changes occurring in the systemic arteries. At times, however, these sporadically distributed nodules are more extensive, showing actually atheroma and calcification, and, as in

the case of Ruppert, leading to a narrowing in some of the branches. Somewhat similar cases are reported by White, Kidd, McPhedran, and Mackenzie. On the other hand, Thorel believes that the pulmonary scleroses differ essentially from those occurring in the aorta and that they are rather of a character of medial sclerosis due to calcium metastasis. Several cases have been described in which this condition of medial degeneration with but little intimal sclerosis has been the main finding.

It would appear, however, that as the arteries of the lesser circulation differ in no essential way from the systemic vessels and the influences brought to bear upon them are, in many respects, similar, the lesions occurring in them are comparable. This view is taken by Torhorst and Ehlers. To these we will refer again.

We have undertaken the histological examination of the pulmonary arteries of the case in question and have further compared the lesions observed in it with the nodular variety which is more commonly encountered in elderly persons.

Before entering upon the essential points in these pathological processes it is necessary to briefly indicate the histology of the pulmonary artery. The structure of these vessels we have found to compare closely with the description given by Torhorst, and his anatomical arrangements will be used as the basis upon which the arteriosclerotic changes are discussed in this paper.

The normal structure of the pulmonary artery and its main branches simulates very closely the architecture of the aorta. The outermost coat is represented by an adventitia consisting of a loosely arranged fibrous tissue interspersed by some elastic



fibers and having occasional longitudinal bundles of muscle fibers scattered through it. Nutrient vessels of different sizes course through its loose connective tissue. Closely applied to its inner border is the media characterized by many strong elastic fibers, circularly disposed, and between them are muscle cells set at all angles, but principally having a circular direction. Along the inner border of this laminated coat is the musculo-elastic layer running longitudinally to the vessel, but whose individual muscle bundles crossing each other at acute angles form a net work. This musculo-elastic layer also contains elastic fibers, which along its inner border are aggregated into a denser bundle to form the inner boundary between this layer and the intima proper. The intima which is the innermost layer has, in the main, a circular direction and is made up of connective tissue, but is rich in fine elastic fibrils often giving the appearance of strong elastic tissue fibers. In the small arteries both the musculo-elastic and connective tissue layers are thin and weak.

Although our study deals more particularly with the changes in the pulmonary artery, we have added some of the history as well as a detailed description of the lungs, so that the points bearing upon the etiology of the pathological processes may be appreciated.

Mrs. X, age 39. The patient's family and previous history were negative. She claimed to have been well until a year ago. She was married and had nine children, three of whom died in infancy. She had one miscarriage of twins seven months old, just before the onset of her present illness, and has not menstruated since. She has always worked hard and her habits of life have been good; she denied lues.

Her present illness began with the miscarriage, for upon getting up after this confinement, December 25, 1909, she noticed her feet and ankles were swollen. This condition progressed and in three days her feet and legs were excessively swollen as far as the knees, so that she thought they would burst. Then the abdomen began to swell and at the end of a week "was filled as tight as a drum." She then went to a hospital, where she remained for five weeks, with no benefit, except that the swelling of her feet and ankles somewhat subsided. This œdema returned as soon as she got up, and she again returned to the hospital for two weeks, and later again for six weeks, but did not improve. Since June 3, 1910, she has been at home. Ever since the miscarriage she has been cyanotic, especially about the face, and worse when she was on her feet. About three months previous to exitus she began to be troubled with pain and soreness in the liver region and entered the Mercy Hospital. These symptoms were severe and for the last three weeks of her life she suffered continuously. No history was obtained of a previous acute intrathoracic lesion.

*Autopsy.*—No. 60, November 27, 1910. Dr. S. R. Haythorn.

The body was that of a well-developed woman, 146 cm. tall. The tissues of the face, ears, lips and extremities had a purplish-blue appearance as of venous congestion. The sclera were slightly jaundiced. Large distended veins were present over the lower portion of the abdomen, as well as on the lower extremities. There was an œdema of the lower abdomen and extremities.

In the thorax extensive adhesions were found in the right pleural cavity, almost completely obliterating it. The right lung was very small and was crowded towards the vertebral border, and was firmly held in this position by the adhesions. The left pleura was free and the lung appeared of more than normal size. The pericardium contained over 300 cc. of a clear fluid.

Heart: Weight 385 gm. Over the right auricle and ventricle

were several milk spots, the largest being 1.5 cm. in diameter. The right auricle was much dilated, and the right auricular appendix contained a laminated red and gray clot. The coronary sinus appeared to be dilated at its mouth. The cavity of the right ventricle was large and the muscular wall appeared quite thick (12 mm.). The papillary muscles in the right ventricle looked like those of the left heart. The whole structure of the right heart was hypertrophied. The tricuspid and pulmonary valves were all thin and leaf-like, showing no evidence of sclerosis. The base of the pulmonary artery showed some diffuse and nodular thickening of the intima, with some areas showing deep fatty change. The left heart was well contracted and the cavities were empty. Both auricle and ventricle appeared of the usual size and showed no definite change. The mitral valve was a little grayish and slightly thickened. The aortic leaflets appeared healthy. The base of the aorta showed a few small nodules of sclerosis close to the openings of the coronary arteries. The coronary arteries showed no evidence of sclerosis. The foramen ovale was patent. The arteries



FIG. 1.—Left lung, showing marked sclerosis of pulmonary arteries.

of the systemic system showed only occasional and slight sclerosis at the points of bifurcation.

**Left Lung:** The organ was diffusely enlarged and appeared over-distended. It was free from adhesions and the outer surface was marbled by a considerable deposit of coal pigment. Over the pleura were a considerable number of white and well-defined lines following the course of the lymphatic channels. The organ crepitated throughout. There was no evidence of consolidation or of tuberculosis. The cut surface of the lung presented a very remarkable appearance, in that the blood vessels in both lobes stood out very prominently, giving them, at first sight, the appearance of bronchi. The main trunk of the left pulmonary artery was irregularly thickened and the intima was quite nodular. The thickening, though nodular, was diffuse and affected the circumference of each vessel. Many of the vessels were of cartilaginous hardness. In places the lumen of the artery was distinctly narrowed, while in other places small pouches occurred in the course of the vessel and particularly at the points close to a bifurcation.

**Right Lung:** The surface of the organ was covered by extensive old adhesions. The organ was very small and collapsed and formed a little shrunken mass lying in the upper and inner part of the chest cavity. This lung was meaty in character, and contained but little air. The tissues were, in part, firm and somewhat fibrosed. There was no evidence of tuberculosis. The bronchi were small and quite pale. The pulmonary arteries were thin-walled and no evidence of sclerosis could be observed in any of them. The lung on section showed no evidence of consolidation, but the lung tissue was tough and almost airless. There was a fair amount of anthracotic marbling through this organ.

In the remaining parts of the body no important findings were made other than the presence of a considerable ascites and a congestion of the veins in the abdomen and extremities. No evidence of any chronic infective process or of syphilis was obtained.

The microscopical examination of the right lung showed a condition of collapse of the alveoli, with a thickening of the alveolar walls. The lining cells of the air sacs were prominent and frequently were of a cuboidal nature. A considerable number of desquamated cells were present within the alveoli. Besides a general thickening of the alveolar walls, small patches of fibrosis were found scattered through the lung tissue. The vessels showed a fair amount of carbon pigment surrounding them, but their walls were unchanged. There was no evidence of old or recent inflammatory reaction within the essential tissues of the arteries, although some of them showed fibrosis of the stroma in which they rested. Here and there this fibrous tissue contained small collections of lymphocytes. Nodular endarteritis was entirely lacking in the vessels of this lung.

In the left lung the alveoli were large and distended. They were, in the main, free from exudate, save some small collections of leucocytes close to some small bronchi. The alveolar walls were quite thin. The striking feature throughout the structure of this lung was the extensive and irregular nodular thickening of the arteries. This thickening was not accompanied by any change in the lung tissue immediately surrounding the arteries, although the large vessels were accompanied by a fair amount of fibrous tissue and anthracosis. The thickening was confined to a reaction in the intima, the media and adventitia remaining undisturbed as far as the microscopical examination could determine.

The remarkable unilateral sclerosis of the pulmonary artery associated with collapse and fibrosis of the lung on the opposite side, as well as with a decided hypertrophy of the right heart, led us to study more minutely the changes in the pulmonary arteries. As has been above described, the thickening of the pulmonary arteries was diffuse and nodular, and macroscopically it appeared that the nodular change was only a more intense and localized condition of the diffuse intimal sclerosis. Portions of the pulmonary artery were selected from different areas in the left lung so that the histological characters of the sclerosis might be studied in all its phases.

#### MICROSCOPICAL EXAMINATION OF PULMONARY ARTERY.

**Main Branches:** The microscopical examination of the pulmonary arteries immediately revealed the fact that an important change had occurred in the intima. In the areas where the thickening was of a diffuse nature the media and adventitia were quite loose and devoid of any evidence of inflammatory infiltration. The nutrient vessels were not increased in number, but many of them showed some narrowing of their lumen. The outer two-thirds of the media was regularly disposed with alternating layers of elastic fibers and muscle cells. On the other hand, the inner layer of the media was somewhat changed through the loss of muscle fibers and the more close packing together of the elastic strands.

In this situation the areas previously occupied by the muscle cells now showed the presence of granules of a fatty nature. Thus with the sudan stain a narrow layer of fatty degeneration affecting the muscle fibers of the innermost zone of the media was easily demonstrated, and the reaction and degeneration were more evident here than in the diffusely-thickened tissues of the intima. This, however, was not the case where the intima showed nodular thickening, in which the extensive degenerations were found in the deep portion of the intima.

The internal elastic lamina was, for the most part, broken up into a multitude of fine fibrils. Intermingled with these elastic fibers was a varying amount of muscle tissue having a longitudinal direction. For the most part, there was some increase in the quantity of the muscle tissue in this layer. More or less fatty degeneration was also present in these muscle cells, but where the intima was only moderately and diffusely thickened the amount of fatty change was not great.

The diffuse thickening of the intima proper was mainly the result of a hyperplasia of the connective tissues and elastic fibrils lying between the endothelium and musculo-elastic layer. Nevertheless, occasional strands or small bundles of muscle tissue were

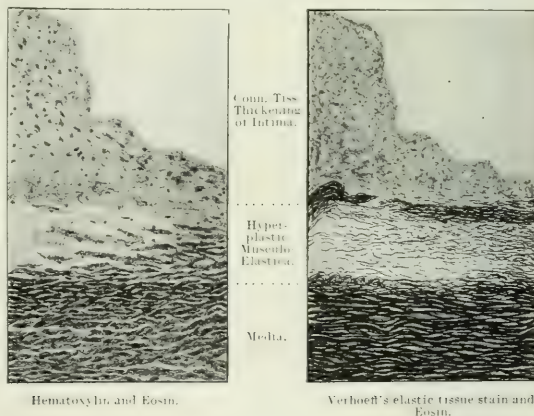


FIG. 2.—Sclerosis of pulmonary artery, showing hypertrophy of musculo-elastic layer and hyperplasia of connective-tissue layer of intima.

found to extend into this layer from the deeper musculo-elastic lamina. The connective tissue thickening consisted of a compact layer in which the connective tissue cells were longitudinally disposed, and, in places, were quite regularly arranged in layers. In other places, again, this connective tissue appeared looser and the cells had a more stellate appearance. The matrix in which the connective tissue cells rested was hyaline in appearance, which sometimes took on an oedematous character.

The nodular thickening of the arteries was a process lying entirely on the inner side of the internal elastic lamina, in which a reaction of both proliferation and degeneration was evident. The proliferative change consisted chiefly in a thickening of the connective tissue beneath the endothelium, in which relatively few elastic fibers were to be found. This hyperplasia was made up of spindle-shaped cells which were arranged more or less loosely and in a parallel manner. Where the tissue was less compact the cells had stellate characters. Near the surface this newly developed connective tissue was well retained and showed no evidence of degeneration. Close, however, to the boundary between intima and

media, extensive fatty change involved the various elements including the muscle and elastic fibers of the immediate vicinity. This process of degeneration was not alone to be observed in the intima, but extended into the media for a short distance. Thus in the vicinity of the musculo-elastic layer no definite structure could be made out, but there atheroma was involving the several tissues. For the most part these nodular areas were similar, but it was observed that some of them gave distinct evidence of inflammatory cells, mainly lymphocytes, scattered through them. It was also observed that the adventitia opposite these nodular areas showed some slight inflammatory reaction in the vicinity of the vasa vasorum. Furthermore, where the nodular thickening of the intima was extensive, the media was thinner than in the remaining portion of the vessel wall.

**Small Branches:** In examining the lung tissue, extensively sclerosed arteries and arterioles of small size are encountered. In fact, throughout the lung tissue, wherever small arteries are met with, sclerosis of their structure is found. This sclerosis simulates in every respect the changes observed in the larger arteries. The

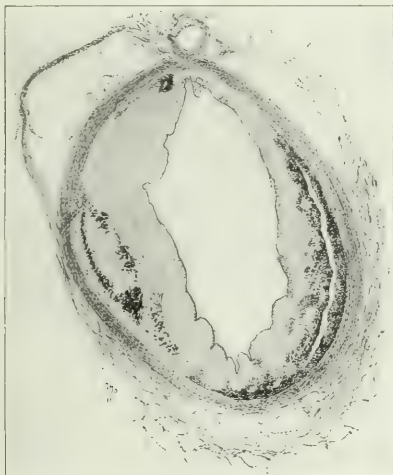


FIG. 3.—Sclerosis of branch of pulmonary artery, showing intimal thickening with deep fatty degeneration.

lesion is for the most part confined to the intima and is of proportionately greater extent than in the large vessels. The lumen is greatly reduced and the architecture of the internal layer much altered. The adventitia and media show relatively little change save that here and there a slight amount of inflammatory infiltration can be seen near the nutrient vessels. On the other hand, the internal elastic lamina and all that lies within it are much altered. The internal elastic lamina commonly shows a splitting into multiple layers, but there is no evidence of any extensive formation of elastic fibrils on the tissue of the greatly thickened intima. There is a thick layer of connective tissue between the musculo-elastic layer and the lumen. The amount of this connective tissue varies in each vessel, as well as on different sides of the same artery. In every instance much atheroma is found in the deep portion of the newly formed tissue, and this fatty change of the intima has also extended into a portion of the media. Inflammatory cells, mainly of the nature of lymphocytes, associated with a few polymorphonuclear leucocytes and plasma cells, are also seen. The musculo-elastic

layer shows an irregular amount of hypertrophy, as well as evidence of degeneration. The hypertrophy of this layer does, however, not make up for much of the wide spread thickening observed throughout the arteries. This hypertrophy of the musculo-elastic layer is not uniform and, in places, is wanting.

**Arteries of Right Lung:** Sections made of the various arteries in this organ showed a normal structure to be present in all of them. Only very occasionally in some of the large branches were some microscopic evidences of an increase in the connective tissue layer of the intima observed. The media and the adventitia appeared normal, there being no evidence of inflammation or sclerosis. No evidence of degeneration was evident in any portion of the pulmonary artery of the right lung.

To resume, the case was one of a woman, aged 39, who died with symptoms of failure of the right heart, with chronic passive congestion, ascites and oedema, in less than a year after a twin pregnancy, which ended in a miscarriage at the seventh month. In addition to the clinical findings, the autopsy revealed a hypertrophied right ventricle and a completely collapsed right lung with firm old pleural adhesions rendering



FIG. 4.—Sclerosis of small branch of pulmonary artery.

this lung almost, if not completely, incapable of functioning. The left lung showed some compensatory emphysema and an arteriosclerosis of the pulmonary arteries, which was distributed throughout both lobes. The extensive arteriosclerosis began at the left pulmonary artery and was distributed as a diffuse and nodular disease throughout its branches. The disease was one of the intima in which hypertrophy of the musculo-elastic layer was commonly found, while an extensive connective tissue proliferation underneath the endothelium had led to much irregular distortion and narrowing of the lumen. The hypertrophy in these tissues was followed by a considerable fatty degeneration which involved the tissues of the intima and sometimes attacked the neighboring media. The elastic tissue showed little evidence of proliferation, but the internal elastic lamina was broken up into multiple strands. The narrowing of the lumen was in some instances very extensive, and simulated the sclerotic condition of the arteries of the systemic



tree, showing endarteritis chronica deformans. Not uncommonly the process of hypertrophy of the musculo-elastic layer, hyperplasia of the sub-endothelial connective tissue and extensive fatty degeneration were to be observed in the same specimen. None of the vessels showed lesions which simulated syphilis.

In view of the absence of syphilis in any part of the body, as well as evidence of any definite infective process to which the unilateral arteriosclerosis could be ascribed, the actual condition found in the respiratory system is worthy of close consideration. We have evidence in the hypertrophy of the right heart of an increase in the resistance of the blood flow through the lesser circulation and in explanation of this we have the presence of an almost completely collapsed right lung of some time standing. The presence of fibrosis within this organ, as well as the firm bands of connective tissue which bound it down, were instrumental in impeding the blood flow through this lung. It is interesting to note that with the diminishing circulation in this organ no reaction of the nature of compensatory hypertrophy of the intima of the pulmonary arteries of the right side, as would be expected from the theory of Thoma, was found. Here we had every condition making for a slowing of the blood stream and for a disproportion between the blood content and the vessels' walls, and yet no definite organic change developed. On the other hand, the left lung responded in a compensatory emphysema to the respiratory incompetence of the organ on the right side. Moreover, the pulmonary circulation was very much disturbed by the collapse of the right lung, so that a greater amount of blood was required to pass through this one organ. It is probable, although this is not entirely proved in this case, that the blood pressure in the right pulmonary circulation was increased. The hypertrophy of the right heart is an evidence of this. This increased blood pressure was mainly borne by the vessels of the lung, which was functioning in an excessive degree.

For comparison we have examined five other cases in which minor scleroses, usually of the nature of isolated plaques, were found irregularly scattered through the main arteries. In two of the cases the arterial changes consisted of a connective tissue thickening of the superficial intima without showing any evidence of proliferation in the musculo-elastic layer, or any sign of degeneration. The findings in these vessels appeared to be only incidental to the cause of death and the post mortem findings. In the three other cases not only was a connective tissue proliferation observed along the inner border of the intima, but in each there was found an hypertrophy of musculo-elastic layer, with more or less evidence of degeneration in this tissue. These latter cases were associated respectively with (1) heart, kidney, and arterial disease, (2) recurrent heart disease, and (3) chronic heart disease with gonorrhoeal polyarthritis. It would appear that, when circulatory disturbances are such that an alteration in the blood pressure of the pulmonary system is brought about, an hypertrophy of the musculo-elastic layer is an early response to this change. On the other hand, nodular thickenings may also occur in the pulmonary system simulating the chronic endo-

arteritis of Virchow. It would thus appear that the pulmonary arteries respond in a manner quite similar to the arteries of the systemic circulation.

Both Torhorst and Ehlers concluded that degenerative changes in the pulmonary artery begin in the musculo-elastic layer, simulating the reaction which Jores described for the aorta. Just as Jores indicated the development of two different types of reaction, the "hyperplastic intimal thickening," involving the musculo-elastic layer and the inner elastic lamella, and the "regenerative connective tissue increase of the intima," originating in the innermost layer, so have all investigators of the scleroses of the pulmonary arteries described reactions of a like kind. Ehlers' studies on pulmonary arteriosclerosis led him to conclusions in agreement with those of Jores, namely, that the connective tissue thickening of the intima commonly followed upon a primary degeneration of this hyperplastic musculo-elastic layer. This, on the other hand, Torhorst did not find, but he believed that the connective tissue thickening of the intima which brings with it a rich supply of fine elastic tissue was primary and together with the hyperplasia of the musculo-elastic layer formed the reaction in response to the increase in blood pressure. These two types of reaction, or according to some, these two stages of the same reaction, which resemble very much those reactions of the aorta named by Jores, "hyperplastic intimal thickening," and "connective tissue increase of the intima," are processes which take place in two different layers, normally seen in the large arteries of the lesser circulation. The first type, which corresponds to the "hyperplastic intimal thickening," consists of an hypertrophy of the musculo-elastic layer, or the "longitudinal layer" of Ehlers, with a change in the internal elastic lamella. The muscular elements increase and the elastic tissue becomes more abundant, and by the crowding together of the elastic tissue fibrils the appearance of newly developed strong fibers becomes marked. This may occur without any involvement of the internal elastic lamina, but usually the hypertrophy of the muscular elements results in a splitting of the strong elastic fibers, with the result that more fine ones come to view, giving the appearance of an equal amount of elastic tissue, spread over a greater area. The second type of sclerosis, which corresponds to the "connective tissue increase of the intima," consists of an increase of the innermost connective tissue layer of the intima. This layer may become thicker as a result of the proliferation of sub-endothelial connective tissue and may or may not be rich in fine elastic tissue fibrils. The connective tissue may increase out of proportion to the elastic tissue and result in a considerable intimal thickening, comparatively poor in elastic tissue fibrils, or even free from them along the inner edge. On the other hand, the elastic tissue of the innermost layer may increase to an unusual extent, resulting in the crowding together of the fine fibrils and giving the appearance of stronger ones in a comparatively thin margin of tissue. Fatty degeneration, though undoubtedly starting in the musculo-elastic layer and probably in the muscle cells or the new formed connective tissue, may spread both inward and outward and involve both intima and media. Later the intima

may show a type of hyaline degeneration and this without much thickening.

In view of these observations the question arises whether one can definitely determine whether the thickening of the innermost layer of connective and elastic tissue or the hypertrophy of the musculo-elastic layer was primary to the degeneration, as observed in our case of blood pressure sclerosis of the pulmonary arteries. The microscopical study showed both types of change to be present, the hypertrophy of the musculo-elastica, with splitting of the fibers of the internal elastic lamina, being the most striking. However, in most of the areas of degeneration there was a great excess of connective tissue in the overlying layer, and it was shown that the nodular eminences observed macroscopically were due to this thickening of the innermost layer.

To sum up, all the cases studied showed plaques on the pulmonary arteries having a gross appearance more or less resembling each other, but differing slightly in color and extent of distribution. In our first case were observed conditions which indicated increased blood pressure as a possible etiologic factor, but in all the others no definite etiology could be assigned, and they are probably examples of the common types of arteriosclerosis of the pulmonary arteries, associated with some general arterial or other changes as a result of systemic processes. In both the former and the latter the type seen in the pulmonary arteries was comparable to the "hyperplastic intimal thickening," and of the type related to the "regenerative connective tissue increase of the intima," as described by Jores for the aorta.

As the intimal changes in our principal case were so advanced, it is impossible to say which of the proliferative reactions was primary. In none of the vessels was a pure form of proliferation of either the superficial or deep intimal layer to be found. It was, however, evident that the process of degeneration began in the hypertrophied musculo-elastic layer and from here extended into the connective tissue thickening, as well as into the media. Nevertheless, it is quite possible that the presence of the deep degeneration in the intima acted as a stimulus calling forth a still further proliferation in the overlying connective tissue. We believe, however, that, like the reaction in the systemic arteries, the hypertrophy of the musculo-elastic layer was the result of the abnormal circulation in the one lung following upon an impeded circulation on the opposite side. The process of degeneration was secondary to the proliferative reaction.

In conclusion, I wish to express my appreciation of the privileges I have enjoyed at the Pathological Laboratory of the University of Pittsburgh, and to thank Dr. Oskar Klotz for the many courtesies I have received.

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## THE VALUE OF NASO-PHARYNGEAL SURGERY IN THE TREATMENT OF CHRONIC EXUDATIVE OTITIS MEDIA.<sup>1</sup>

By H. O. REUK, M. D., Baltimore, Md.

That chronic exudative otitis media, with its characteristic tendency to progressive deafness, has for its principal cause and continuous exciting factor some abnormality in the nose, pharynx or naso-pharynx—such as hypertrophied turbinates, deflected septum, hypertrophied or submerged diseased tonsils, or adenoids—is an accepted fact, probably settled beyond dispute. The relationship between the naso-pharyngeal condition and the commencing or progressing middle ear disease seems to have been thoroughly established and requires no special argument at this time. It is also an accepted fact that the early correction of such abnormalities is good prophylactic medicine, in that it tends to prevent the occurrence of affections of the middle ear. Furthermore, it seems to be the general belief that even after an acute exudative otitis media is established the ear can be restored to a normal condition and safeguarded for the future by prompt and proper treatment of the exciting factors in the nose or throat.

Assuming all this to be true, the possibility of curing or

relieving an exudative otitis media that has reached the chronic stage, by removal of the naso-pharyngeal trouble, is not the subject of such universal agreement. As a matter of fact, there exists an attitude of skepticism in regard to any and all treatment of chronic exudative otitis media, on the part of the profession as well as of the public. There is abroad a false notion that this diagnosis always carries with it a hopeless prognosis as regards the auditory function and that the unfortunate patient is necessarily condemned to ultimate deafness, the rate of progress downward being more or less rapid according to circumstances. We must admit that there are many persons suffering with this affection for whom we can do little or nothing either in the way of curing the disease or of preventing its steady advance, but I am sure there are many more to whom the optimistic, skilled and patient attendant can render most helpful service. It is, however, not within the province of this paper to discuss the various forms of treatment that may be useful under the different conditions observed nor even to offer a classification of these variations. The single topic for present considera-

<sup>1</sup> Presented at the meeting of the American Otological Society, at Washington, May 7, 1913.

tion might be embraced in the question: What effect upon the ear can one logically expect from naso-pharyngeal surgery when the chronic exudative otitis media is believed to have had its origin in, or to be still excited by, abnormal conditions in the nose and throat?

I was led to ask myself this question several years ago for the following reasons: In the first place, I had found that some observers were doubtful of securing beneficial results to the ear from these operations and their doubts were based upon practical experience rather than disbelief in the theories upon which the treatment rested; for instance, cases which had presented every evidence of relationship between the aural and naso-pharyngeal affection had not been improved nor relieved, in so far as the ears were concerned, by the operation performed. As I shall attempt to show later, I think that many of these failures can be explained and that the doubts, though justified, were misplaced. Secondly, I desired to determine for myself a proper line of conduct toward these patients. Granting the existence of some naso-pharyngeal abnormality in association with a chronic otitis showing advancing deafness, what right had I to advise an operation within the nose or throat, when possibly these organs were not directly suffering, and what hope could I honestly and conscientiously hold out to the patient that such an operation would benefit his aural condition?

With a view to arriving at a definite answer to these questions, I have during the past few years carefully studied a series of such cases and it is to some conclusions drawn from these observations that I particularly wish to ask your attention. The small series of 34 cases upon which I shall report is taken entirely from my private practice; I have not attempted to study the records of those hospital and dispensary cases that were treated during the same period of time, because it is so difficult to follow up such cases in order to observe results and to keep the records accurate. In character the cases here under discussion are limited strictly to simple, chronic, exudative (catarrhal) otitis media associated with and believed to be dependent upon some naso-pharyngeal abnormality. No case is included which presented other complications, that is, such as involvement of the auditory nerve, otosclerosis, or the history of hereditary deafness.

A comparison of the conditions before and after treatment must unfortunately depend upon subjective tests and it is quite difficult to establish a test which shall be reasonably accurate and reliable and not subject to variations due to the personal equation of either the examined or the examiner. In every case the routine hearing tests were made, but most of these are of little value for comparison, with the object of answering the question propounded. The important facts to ascertain were whether or not the hearing was improved, remained stationary or had become worse immediately after the operation (meaning within two weeks), and, what the relative condition of hearing would be at a considerably later period. In looking over my records it still appears to me that the one and only test that could be utilized is one that I early came to look upon as the most practical and which might be

called a self-controlled tuning-fork test. This fork, devised by Dr. Clarence J. Blake, and manufactured at the Lawrence Scientific School of Harvard University, is of the middle register ( $C^2 = 512$  v. s.). It is set in action by drawing the prongs between the thumb and forefinger of one hand so that the tips are brought together by this pressure and spring apart of their own volition as they escape from pressure. The particular fork which I have used, and which has been repeatedly tested, can be heard by the normal ear for exactly 20 seconds when held at a distance of one inch from the meatus. It seems to me that this method is not open to the objection that applies to other means of setting a tuning fork in motion, such as striking it upon some object or with some form of hammer. No matter how much pressure is exerted the prongs can only be brought into contact and no matter how quickly released they can only spring apart; it is therefore scarcely, if at all, subject to any control upon the part of the examiner.

Perhaps it should be mentioned, too, if merely as a matter of acknowledgment, that what might be called a theoretical improvement in hearing is not necessarily one of practical value. For instance, ability to hear a moderately high-pitched tuning fork for a few seconds longer after treatment may not mean any greater ability to hear conversation. I used the test only as being the most reliable practical test of scientific value and believe that it fully serves the purpose here of indicating the direction of progress of the aural disease.

The accompanying table sets forth the age of the patient; the abnormal condition observed in the nose, pharynx or naso-pharynx; the duration of time in which the deafness had been increasing; the state of hearing by air conduction for the above named fork, expressed in fractions, the denominator representing the time that the fork should be heard by the normal ear and the numerator showing the time that it was actually heard; the operation performed; the immediate effect upon the hearing, according to the same test made within two weeks of the date of operation; and the condition of hearing, according to the same test, at the latest period thereafter that the patient was seen—which varied from six months to five years. The complaint in every case was increasing deafness and the period of time during which this had been observed varied from six months to fifteen years. Curiously enough, this longest-existing trouble (case No. 25) was one of those showing most marked improvement as the result of an operation.

Examination of this chart will show that in 32 cases there was immediate improvement of hearing to some degree; that in two cases there was no apparent change; that in none was there any immediate loss of hearing. A study of the later observations will show that of these 32 cases 26 remained improved, 4 showed additional improvement, and only 2 lapsed back from the first improvement to the previous state of hearing.

From a consideration of these cases I feel fully justified in answering my question with the following statement: Correction of the naso-pharyngeal abnormalities referred to—



hypertrophied turbinates, deflected septa, hypertrophied or submerged diseased tonsils and adenoids—in uncomplicated cases of chronic exudative otitis media will almost certainly check the advance of the aural disease, arrest progress of the deafness, and, in some instances, result in improvement of the hearing. It is impossible to predict in any given case that much improvement of hearing will follow and I am, in consequence, unwilling to hold out to any of these patients the hope of reclaiming any part of the lost hearing power. I usually tell them now that there is a reasonable certainty that further deterioration can be prevented; that there is a possibility, but not a strong probability, of reclaiming some part of what has been lost; and I usually find they are quite satisfied with the assurance that the disease can be arrested.

gist's point of view, the removal of these abnormalities must be accomplished in a manner thorough and complete, without injury to neighboring normal structures and with the object of restoring the parts to a normal anatomical and physiological status. Now of what avail is a nasal operation that results in an adhesion between the septum and the lateral wall? It would have been better to leave that turbinate or spur alone, for the nasal condition has not been improved, and, most certainly, no good effect upon the ear could be expected. An operation upon the tonsils which results in ablation of the faucial pillars (containing the palato-glossus and the palato-pharyngeus muscles) has, of course, disposed of the tonsils, but it can scarcely be expected to improve the function of the tubal muscles.

No.	Age, years.	Naso-pharyngeal abnormality.	Duration of increasing deafness.	Hearing for fork: (1 = 512 v. s.)	Operation.	Immediate hearing result.	Permanent hearing result.
1	39	Large adenoid, obstructing the tubal orifices.	Several years.	R. 18/20, L. 5/20.	Adenoidectomy.	R. 13/20, L. 19/20.	R. 17/20, L. 12/20, 2 yrs. later.
2	32	Hypertrophied rt. inf. turbinate; fibrous bands in Rosenmüller fossa.	2 years.	R. 8/20, L. 3/20.	Turbinectomy and removal of bands.	R. 10/20, L. 10/20.	Same, 6 mos. later.
3	24	Fibrous bands across left fossa of Rosenmüller.	6 months.	R. 20/20, L. 10/20.	Removal of bands.	R. 20/20, L. 15/20.	Same, 3 yrs. later.
4	35	Diseased submerged tonsils.	1 year.	R. 12/20, L. 7/20.	Tonsillectomy.	R. 15/20, L. 10/20.	Same, 6 mos. later.
5	14	Hypertrophied tonsils and adenoid.	1 year.	R. 15/20, L. 10/20.	Tonsillectomy and adenoidectomy.	R. 20/20, L. 16/20.	Same, 12 mos. later.
6	14	Hypertrophied tonsils and adenoid.	1 year.	R. 15/20, L. 10/20.	Tonsillectomy and adenoidectomy.	No change.	No change.
7	17	Submerged tonsils and scar tissue.	Several years.	R. 5/20, L. 5/20.	Removal of tonsils and scar tissue.	R. 10/20, L. 8/20.	Same, 1 yr. later.
8	24	Deflected septum.	3 years.	R. 7/20, L. 1/20.	Submucous resection.	R. 14/20, L. 5/20.	Same, 1 yr. later.
9	18	Hypertrophied turbinates.	8 months.	R. 15/20, L. 15/20.	Turbinectomy.	R. 20/20, L. 20/20.	Same, 6 mos. later.
10	19	Hypertrophied rt. inf. turbinate.	2 years.	R. 10/20, L. 15/20.	Inf. turbinectomy.	R. 17/20, L. 17/20.	Same, 1 yr. later.
11	28	Deflected septum.	6 months.	R. 15/20, L. 12/20.	Submucous resection.	R. 19/20, L. 10/20.	Same, 1 yr. later.
12	24	Adenoid tissue about tubes.	5 years.	R. 7/20, L. 7/20.	Adenoidectomy.	R. 15/20, L. 10/20.	Same, 6 mos. later.
13	21	Intumescent rt. inf. turbinate. Hypertrophied lt. middle turbinate.	3 years.	R. 20/20, L. 5/20.	Middle turbinectomy.	R. 20/20, L. 9/20.	Same, 3 mos. later.
14	23	Hypertrophied middle turbinates.	Several years.	R. 12/20, L. 3/20.	Turbinectomy.	R. 15/20, L. 8/20.	Same, 2 mos. later.
15	18	Hypertrophied tonsils.	1 yr. 6 mos.	R. 12/20, L. 10/20.	Tonsillectomy.	R. 14/20, L. 15/20.	Same, 7 mos. later.
16	26	Hypertrophied inf. turbs. and adenoid.	3 years.	R. 15/20, L. 12/20.	Inf. turbinectomy and adenoidectomy.	No change.	No change.
17	32	Tonsil masses, previously burned.	3 years.	R. 17/20, L. 5/20.	Tonsillectomy.	R. 17/20, L. 9/20.	Same, 1 yr. later.
18	31	Hypertrophied tonsils.	1 year.	R. 15/20, L. 2/20.	Tonsillectomy.	R. 20/20, L. 20/20.	Same, 1 yr. later.
19	28	Submerged tonsils.	1 year.	R. 17/20, L. 10/20.	Tonsillectomy.	R. 20/20, L. 13/20.	Same, 6 mos. later.
20	18	Hypertrophied tonsils and adenoid.	4 years.	R. 20/20, L. 8/20.	Tonsillectomy and adenoidectomy.	R. 20/20, L. 15/20.	Same, 1 yr. later.
21	25	Adenoid.	7 years.	R. 18/20, L. 17/20.	Adenoidectomy.	R. 18/20, L. 18/20.	Same, 6 mos. later.
22	10	Hypertrophied tonsils and adenoid.	12 years.	R. 5/20, L. 1/20.	Tonsillectomy and adenoidectomy.	R. 15/20, L. 10/20.	Same, 2 yrs. later.
23	27	Diseased submerged tonsils.	Several years.	R. 8/20, L. 1/20.	Tonsillectomy.	R. 13/20, L. 15/20.	Same, 6 mos. later.
24	18	Hypertrophied turbinates.	Several years.	R. 10/20, L. 6/20.	Inf. turbinectomy.	R. 15/20, L. 15/20.	Same, 6 mos. later.
25	26	Hypertrophied middle turbinates.	15 years.	R. 6/20, L. 6/20.	Middle turbinectomy.	R. 18/20, L. 15/20.	Same, 6 mos. later.
26	32	Submerged right tonsil and hypertrophied rt. inf. turbinate.	4 years.	R. 10/20, L. 12/20.	Tonsillectomy and turbinectomy.	R. 20/20, L. 20/20.	Same, 3 mos. later.
27	39	Intumescent inf. turbinates.	Several years.	R. 15/20, L. 2/20.	Cauterization of inf. turbinates.	R. 17/20, L. 17/20.	Same, 6 mos. later.
28	33	Degenerate submerged tonsils.	3 years.	R. 10/20, L. 7/20.	Tonsillectomy.	R. 19/20, L. 13/20.	Same, 1 yr. later.
29	26	Hypertrophied turbinates.	7 years.	R. 5/20, L. 5/20.	Cauterization of turbinates.	R. 10/20, L. 10/20.	Same, 1 yr. later.
30	24	Submerged tonsils.	5 years.	R. 8/20, L. 1/20.	Tonsillectomy.	R. 15/20, L. 15/20.	Same, 6 mos. later.
31	19	Hypertrophied tonsils and adenoid.	2 years.	R. 15/20, L. 10/20.	Tonsillectomy and adenoidectomy.	R. 18/20, L. 15/20.	Same, 6 mos. later.
32	16	Hypertrophied turbinates.	2 years.	R. 10/20, L. 10/20.	Turbinectomy.	R. 15/20, L. 18/20.	Same, 6 mos. later.
33	22	Hypertrophied tonsils.	15 years.	R. 15/20, L. 7/20.	Tonsillectomy.	R. 18/20, L. 10/20.	Same, 2 yrs. later.
34	29	Diseased submerged tonsils.	10 years.	R. 5/20, L. 10/20.	Tonsillectomy.	R. 8/20, L. 7/20.	Same, 2 yrs. later.

Now, I should like to revert to a consideration of that part of my first proposition which relates to the reason why so many failures and disappointments have followed naso-pharyngeal operations in chronic otitis media. I am convinced that the explanation lies in incomplete or improperly performed surgical procedures. Our conclusion that there is a definite connection between the naso-pharyngeal lesion, as a predisposing or active factor, and the slowly progressive chronic middle ear affection has for its foundation the belief that these abnormalities in the upper respiratory tract interfere with the normal physiological function of the tympano-pharyngeal tube. It matters not whether the effect upon the ear is produced by deflection of the air currents from their natural course through the nares, from mechanical obstruction of the mouth of the tube, from vaso-motor disturbances resulting from chronic inflammation, or from impairment of motion in the musculature of the soft palate and tubes; from the otolo-

During the time that I have been collecting the material embraced in this paper I have also had the opportunity of seeing some other cases that served to throw light upon these points. A young lady whom I had advised to submit to a tonsillectomy reported to me a year later that, in consequence of some tonsil surgery that she had witnessed while serving as a nurse at one of our general hospitals, she had so feared the operation recommended that she had preferred "to have the tonsils burned out by electricity." She had been subjected to nine cauterizations with the result that there was a mass of tonsillar and scar tissue to which the anterior and posterior faucial pillars were completely adherent. Not very long ago another patient returned to tell me that she had taken my advice and had her tonsils removed. That much was true, but it was not the whole truth; incidentally, the faucial pillars, on both sides, had been taken away, the operator making a clean sweep. It has even been seriously pro-

posed recently, by a surgeon in one of our large hospitals, that hemorrhage after tonsillectomy could be prevented (not controlled, mind you, but prevented) by suturing the anterior and posterior pillars together over the fossa as soon as the tonsil is removed. Can you think of anything less likely to benefit the middle ear? I can scarcely conceive of any circumstances requiring such suturing of these pillars; it certainly is not necessary either to prevent or control hemorrhage.

If such surgical work as this is performed upon patients suffering with chronic exudative otitis media it is not surprising that the aural disease is not arrested or benefited. Almost, if not quite, as bad as the effect upon the individual victim of such surgery is the fact that such results seriously discredit the work of competent surgeons; the otologist who has not received the right kind of assistance becomes discouraged and discards the only means of helping these patients, while the unfortunate victim goes out to decry all specialists. It goes without saying that I am not criticising any of that large body of our competent confrères working in this field, but every one of us knows that in every city and large town in this country numerous bungling operations of this sort are being performed daily by men without proper surgical training or knowledge of the specialty of rhino-laryngology. We are too frequently seeing or hearing of evil effects from operations in the nose or throat. For instance, of nasal operations that were frightfully painful; of tonsil or adenoid operations attended by profuse or even dangerous hemorrhage;

or of some such injurious results as I have previously referred to. Now, any operation within the nose can be rendered absolutely painless if the cocaine be properly employed; and that does not mean using a large quantity. There is no reason whatsoever for the loss of more than a few drops of blood, a dram at the most, in a properly-performed tonsillectomy. Adenoidectomy is necessarily accompanied by some loss of blood, but even in this operation there need be nothing worthy the name of hemorrhage if a gauze tampon be applied and held in position for a short time immediately after removal of the adenoid. In regard to the tonsillar hemorrhages reported, I am reminded of a phrase I once heard Prof. Halsted use in the course of a lecture, which I cannot quote verbatim, but which was to the effect that hemorrhage in the course of an operation is the sole means the unconscious patient has to rebuke the incompetent or unskillful surgeon.

In conclusion, I desire to set forth emphatically my belief that simple exudative otitis media which is due to abnormal or diseased conditions in the nose or throat can be arrested in its progress by removal of these exciting conditions; that in such cases the progressive deafness can be stopped and further loss of hearing prevented; that in some few cases the hearing power may be materially improved; and that success of this kind depends, however, upon the proper performance of nasopharyngeal operations so that there shall be complete and thorough eradication of the abnormality without injury to neighboring normal structures.

## NOTES ON NEW BOOKS.

*Disease in Milk. The Remedy Pasteurization.* (New York: 1913.)

Mrs. Lina Gutherz Strauss says in her Foreword: "The presentation to the public of this book has a definite purpose, and is animated by a single hope. In calling the attention of others to the life work of my husband I trust that beneficent spirits may be stimulated to go and do likewise and achieve greater things for humanity." We also hope this, but what greater thing for humanity can anyone do than Nathan Strauss did in preventing illness among babies by giving away clean milk during the summer months of many years to the poor of New York city and elsewhere. He saved lives just as much as any doctor ever does, and many more than a single physician ever can and his name should ever be revered and loved for the work he did. It is only the rich who can accomplish such splendid results and were all the rich to employ their wealth to similar noble ends there would not be so many attacks on them, nor would they be so abused.

This collection of papers by Mr. Strauss is a valuable document as demonstrating to communities and individuals what can be done to help to keep babies well during the hot summer months—the cost is but small and the work simple, and it is to be earnestly hoped that others will forward this life-saving work.

*The Operating Room and the Patient.* By RUSSELL S. FOWLER, M.D. Third Edition Rewritten and Enlarged. Illustrated. \$3.50. (Philadelphia and London: W. B. Saunders Company, 1913.)

This is naturally a popular work with a certain body of surgeons and students. It is serviceable for those who have not received a thorough surgical training for it goes into much detail of points which are essential to the good conduct of a surgical

case, and which every man who expects to perform any operations should have at his fingers' ends before he undertakes work of this nature. It has a good index, is freely illustrated—not always in the best taste, however—and covers the ground satisfactorily.

*Epidemic Cerebrospinal Meningitis.* By ABRAHAM SOPHIAN, M.D. Illustrated. \$3.00. (St. Louis: C. V. Mosby, 1913.)

The author had a very exceptional opportunity to study an epidemic of this disease in Texas—especially in Dallas, during 1912; and this work is largely a result of his observations at that time. He describes at length the etiology and symptomatology, then the laboratory diagnosis of meningitis, and its complications, and in two more chapters the results of studies in blood-pressure in meningitis, and treatment. This book which is a comprehensive study of this disease will needs be consulted when other authors are compiling descriptions of it, but for the ordinary student simpler and briefer accounts will suffice. The author has a long bibliography of names, but nowhere is there any reference to where the papers of the writers referred to can be found.

*An Introduction to the Study of Infection and Immunity. Including Chapters on Serum Therapy, Vaccine Therapy, Chemotherapy and Serum Diagnosis. For Students and Practitioners.* By CHARLES E. SIMON, M.D. \$3.25. (Philadelphia and New York: Lea & Febiger, 1912.)

The work is intended to be "an introduction to the study of infection and immunity and of the application of immunological principles to diagnosis and treatment." The first eleven chapters are devoted to a discussion of the general principles of immunity. The way in which micro-organisms injure the body is considered:

and the reaction of the body to this injury with antibody formation. The various "types" of immunity are described and their mechanism explained so far as possible. Ehrlich's hypothesis is extensively discussed.

In the second portion of the book the more practical applications of the subject are taken up. The various methods of immunization applied to man, especially active immunization by the use of vaccines, are well summarized. Especial attention is given to therapy: including the use of vaccines, and of tuberculin: of antitoxin, and other immune serum: and of salvarsan in syphilis. The last chapter is devoted to a too brief sketch of the commoner diagnostic reactions. The Widal reaction and the Wassermann reaction are described in some detail. The tuberculin and leutin reactions are illustrated by several excellent colored plates. On the whole the book is well written and should be of real service, as an "introduction to immunity." It is not detailed enough to serve as a comprehensive laboratory manual.

*Flatulence and Shock.* By F. G. CROOKSHANK, M. D. London. \$1. (New York: Paul B. Hoeber, 1913.)

This thin volume is made up of two lectures which have little connection one with the other. The concluding paragraph of the first and the longer is: "But in strictest confidence, I will tell you this: should any of you, from overwork, overmuch tea, overmuch tobacco, or what not, get a spell of neurotic flatulence, and eructations with air gulping, nothing will give you so much relief as a bottle of the very best crème de menthe, sipped slowly and steadily until you are better," which seems to us pernicious if not dangerous advice. The lecture on Shock is a somewhat popular presentation of the subject, and adds nothing to our knowledge. Any adequate reason for collecting these papers together is not clear.

*Golden Rules of Diagnosis and Treatment of Diseases.* By HENRY A. CABLES, M. D. Second Edition. Revised and Rewritten. (St. Louis: C. V. Mosby Company, 1913.)

The title of the book is pretentious for the diseases treated are only those of the stomach, intestines, liver, gall bladder, pancreas and peritoneum, kidneys and bladder, blood, ductless glands, vascular system, lungs and pleural, and infectious and constitutional diseases. It is "intended to furnish a quick means of ready reference for physicians" and herein lie the dangers of these golden rules, works which we believe do more harm than good. The information given in them may be correct, but no one can really benefit by their use.

*Dreams and Myths. A Study in Race Psychology.* By DR. KARL ABRAHAM, Berlin. Translated by WILLIAM A. WHITE, M. D. Journal of Nervous and Mental Diseases, Monograph Series, No. 15 (New York, 1913.)

In sagas and legends it is a well known fact that folk phantasy finds expression, and in this work an attempt is made to compare myths with the phenomena of individual psychology, especially with dreams. As Freud's psycho-analytic method gradually became elaborated, it was found that a searching investigation of the dream-state was essential for the full understanding of the personality of the individual. According to Freud there lies at the bottom of every dream a repressed wish in the unconscious, and the deepest roots of this wish lie in the childhood of the dreamer. It is very clearly shown, for instance, how the common dream of the death of a near relative can be traced back to an infantile wish, and how erroneous it is to assume that the feeling of the child for its parents, and brothers and sisters is from the first, one of love. The above points are further elaborated and explained in connection with the Oedipus saga.

Abraham takes the Prometheus saga as an example of a symbolic myth, and subjects it to the same method of interpretation as that of a dream analysis. He proves clearly and convincingly how the factors of condensation, displacement, secondary elaboration, and wish fulfillment which are almost invariably present in dreams are also present in the Prometheus saga, and concludes by making the following statement: "As Freud has shown for the Oedipus saga so I believe I have established for the Prometheus saga that it has not taken its origin from ethical, religious, or philosophical considerations, but from the sexual phantasies of mankind."

This book of Abraham's is an exceedingly interesting and stimulating one, and is well worthy of the most careful study by every student of psycho-pathology.

The translation is excellent.

*Solidified Carbon-Dioxide.* By RALPH BERNSTEIN, M. D. Illustrated. (Hammond, Ind.: Frank S. Betz Co., 1912.)

The author is somewhat enthusiastic on the use of solidified carbon-dioxide, as the following quotation from the preface will indicate: "That we have in solidified carbon-dioxide the remedial substance par excellence in the treatment of cutaneous neoplasms, both benign and malignant, cannot now be denied, and which, from clinical evidence, because of its superiority, will eventually take the place of the x-rays and the many inferior chemical substances in common usage."

The principle value of the little book lies in the detailed technic of the preparation and use of solidified carbon-dioxide. There is no doubt of the efficacy of this substance in the treatment of a number of skin lesions, but it hardly seems wise, as yet, to abandon for it all other well established and successful methods of treatment.

J. S. D.

*Clinical Laboratory Methods. A Manual of Technique and Morphology, designed for the use of Students and Practitioners of Medicine.* By ROGER S. MORRIS, A. B., M. D. First Edition. (New York and London: D. Appleton & Co., 1913.)

Medical literature is at present abundantly supplied with books which deal, in a fairly exhaustive manner, with the various topics generally included under the title "Clinical Diagnosis." By their use physicians and students should become familiar with the fallacies, advantages and interpretations of the common and more unusual tests applied for diagnostic purposes. It is not, however, to be expected that anyone will burden his mind with the actual operative details of many of the tests themselves. Indeed, a great part of modern medical education consists in knowing where to find authoritative opinions and reliable methods when needed.

A ready reference library is admirably provided for the busy men who wisely take advantage of the aids which clinical laboratory methods afford to the sciences of diagnosis and treatment, in the book just written by Dr. Morris. As stated by the author, "the significance of the abnormal is not discussed"; the space is simply allotted for the statement of how to apply qualitative tests and quantitative methods of proven value. There has been, moreover, a careful omission of procedures which are in any way too exacting or time-consuming. In many instances several methods are given thus allowing one a free choice. The "sources of error" paragraphs, which follow most of the tests, are invaluable and should make faulty interpretations a negligible quantity. Wherever it has seemed necessary, footnotes give references to valuable original articles or exhaustive treatises. In this manner the subjects of urine, gastric juice, faeces, sputum, blood and puncture fluids have been admirably covered, yet in a book of convenient size, well printed and illustrated by 46 well-chosen cuts, and two colored plates, drawn by the author, depicting the various blood cells as stained by the Ehrlich and Romanowsky methods. The



latter is especially to be commended. Where methods involve calculations, as, for instance, the quantitative determination of urinary chlorides, examples are given which make the successive steps clearly understood.

The style of the book is pleasing and reflects both the author himself and his wide practical knowledge of the subjects treated. Errors are singularly few. Indeed, with the aim of the book in mind, it is hard to see how it could be improved upon. There is no other work like it and the reviewer would earnestly urge its purchase and constant use by those for whom it was preeminently written—practitioners of clinical medicine. S. R. M.

*Müller's Serodagnostic Methods. Authorized Translation from the Third German Edition, 1913. By ROSS C. WHITMAN, B. A., M. D. (Philadelphia and London: J. B. Lippincott Company.)*

This little volume of 143 pages has much to commend it. It is in no sense an exhaustive work, nor does it attempt to discuss the theories upon which many of the described methods are based. It assumes a knowledge on the part of the individual of the fundamental laws and concepts of immunity, and their general application to the wide field of serology. It likewise assumes at least some knowledge and practice in serological technique. "The chief emphasis has been laid on making the description of the various methods as exact as possible, and especially on giving a complete and detailed list of the reagents and apparatus required for each test."

Methods of injecting animals—bleeding them and the preservation of sera—are concisely given. The various diagnostic methods are in general treated under four headings: (a) The principle involved; (b) the field of application for the test; (c) the apparatus required; and (d) the technique of application. Discussions and interpretations of results have been for the most part omitted. Certain tests of doubtful value, such as the cobra venom, Much-Holzmann, and meiostagmin reactions have purposely been included, in the hope of stimulating further work on them and other lines of research which they suggest. Though the book should "lighten the labor of the beginner" or practiced worker in the field of serology, it should only be used in conjunction with others of a more critical and theoretical nature. The possession of such a book will, however, never be regretted. S. R. M.

*Laboratory Methods. With Special Reference to the Needs of the General Practitioner. By DRS. B. G. R. WILLIAMS AND E. G. C. WILLIAMS. Second edition. Illustrated. \$2.50. (C. V. Mosby Company, St. Louis, 1913.)*

The value of this work lies in the fact that it demonstrates that a general practitioner can do a lot of laboratory work at a slight cost and with simple appliances, and there are many practitioners living remote from cities who will find this book a most useful and clear guide in any investigation they may want to pursue. That a second edition of this work has been called for shows how wide awake many of our country doctors are, and how they try to keep up their studies under difficulties. We hope this new and improved edition will have a still larger circulation.

*International Clinics. Vol. II. Twenty-third series. \$2.00. (Philadelphia and London: J. B. Lippincott Company, 1913.)*

The contents of this volume are of the same varied character as those of the preceding volumes; there is both entertainment and instruction to be drawn from these clinics, and one of their most important uses is in making known the various writers to

the many readers. It is a valuable form of instruction—learning to know about men by their writings—and in these volumes one has the opportunity to measure the "bigness" of many contributors, and so learn what to read and what to leave unread.

*Progressive Medicine. Vol. II. June, 1913. (Philadelphia and New York: Lea & Febiger.)*

The review of hernia and surgery of the abdomen consume 186 pages of this volume, gynecology a little over 100, and diseases of the blood, thyroid gland, nutrition, the lymphatic system, and diathetic and metabolic diseases about 115, and ophthalmology not quite 30. These figures are merely noted to show the subjects which seem to receive the greatest attention in the general medical literature. The deduction may not be quite accurate, for those responsible for the different chapters may prepare reviews of very varying length; but there is no doubt that the relative importance of the various subjects dealt with in this volume is fairly represented here, and the readers will, in reading the reviews, get a just impression of the work being done in Europe and America in these lines of science.

*Hygiene and Sanitation. A Text-book for Nurses. By GEORGE M. PRICE, M. D. \$1.50. (Philadelphia and New York: Lea & Febiger, 1913.)*

The field of work for nurses has widened so greatly in the last few years that many books, besides those directly dealing with the care of the sick, are needed for their instruction, and this small volume will be welcome to a large body of women now engaged in various branches of social service work. The author's manual is simple and covers the subject satisfactorily; he discusses tersely the hygiene of dwelling houses, foods, schools, occupations, municipalities, etc., and has written a helpful introduction for broader study of these subjects for those who wish to make themselves proficient in any one of these subdivisions of hygiene.

*Stammering and Cognate Defects of Speech. By C. S. BLUEMEL. \$5.00. (New York: G. C. Stechert and Company, 1913.)*

The author's theory of stammering, that it is due to transient auditory amnesia, has been evolved, in large part, he says, "as the result of introspective evidence; evidence as indispensable as it was uncovered"; and to this theory he devotes the first volume of his work, the second being given over in large measure to a description of "contemporaneous systems of treating stammering: their possibilities and limitations." The second volume thus serves as an historical review of the subject, and contains in addition a glossary of words, the most of which any intelligent reader should understand without looking up, and a very long bibliography. Further evidence, possibly of an experimental nature, will have to be brought to substantiate the author's theory, and meantime psychologists will be interested in applying this idea to a study of their own cases.

*Diseases of the Eye. By GEORGE E. DE SCHWEINITZ, M. D. Seventh edition, thoroughly revised. Illustrated. \$5.00. (Philadelphia and London: W. B. Saunders Company, 1913.)*

Dr. de Schweinitz's work requires no word of commendation from us. Its admirable qualities have long since been recognized by the medical profession, and its seventh edition is but a new proof of its excellence. The author's reputation is world-wide and his book has been for many years one of the standard treatises on diseases of the eye.

# BULLETIN

OF

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## THE DEVELOPMENT OF ANTIBODIES IN THE SERUM OF PATIENTS RECOVERING FROM ACUTE LOBAR PNEUMONIA.

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Of the acute infectious diseases there is none which offers more interesting problems for investigation than acute lobar pneumonia. The remarkable phenomena occurring at the crisis have attracted particularly the attention of investigators. The very abrupt and radical change in the condition of the patient, "from perhaps a state of extreme hazard and distress to one of safety and comfort," indicates that some profound change must suddenly have taken place in the balance between the invading organisms and the defensive forces of the host. The numerous attempts to determine the nature of this change, to work out the mechanism by which recovery naturally occurs, have met with unexpected difficulties.

It is certain that the crisis is not due to an anatomical change in the diseased lung tissue; nor is it due to a sudden loss of virulence on the part of the organism. Rosenow<sup>1</sup> found no appreciable difference in the virulence of strains isolated by blood culture early or late in the disease. Luet-scher<sup>2</sup> studied the comparative virulence of strains isolated from the sputum by plating, before, at, and after the crisis, and found no diminution in virulence for mice as long as actual sputum, from the lung, could be obtained.

Blood-culture studies have shown that death in pneumonia is usually due to the development of a general septicæmia, except in those cases in which some serious accidental com-

plication develops. In favorable cases, on the contrary, the percentage of positive findings and the number of organisms present in the blood diminish as the crisis (or lysis) is approached. Rosenow<sup>3</sup> has shown that the number of viable cocci in consolidated lung tissue, obtained by repeated aspiration, becomes greatly reduced, or disappears during and after the crisis, but he did not demonstrate the mechanism by which they were destroyed.

It is generally agreed that the crisis is brought about by an increase in some of the defensive forces of the body, which prevents the unrestricted multiplication of the organisms; that it marks the development of an immunity which is due to, and associated with, the appearance of antibodies in the serum. That immune substances of some sort are found in human serum at the crisis was first demonstrated by G. & F. Klemperer.<sup>4</sup> They showed that the serum of convalescent patients, like that of immunized rabbits, will protect rabbits from otherwise fatal doses of virulent pneumococci. This has been confirmed by Roemer,<sup>5</sup> and by Neufeld and Haendel,<sup>6,7</sup> who found that some degree of protective power for mice was conferred by all of five sera investigated.

This protective power has since been denied by several other observers. Seligmann and Klopstock,<sup>8</sup> Boettcher<sup>9</sup> (in ten cases), and Strouse<sup>10</sup> (in eight cases), were unable to demonstrate any protective power for mice in postcritical sera. The

failure of the first writers mentioned was probably due to faulty technic, since the doses of culture used were too large, or were not accurately measured. Strouse used carefully graduated doses, but in most of his series, at least, used a virulent stock culture, which may have differed in its serum reactions from the strains infecting the patients whose sera were studied.

Evre and Washbourn<sup>11</sup> were the first to demonstrate clearly such strain differences in pneumococci. They found that, whereas Pane's anti-pneumococcus serum in doses of 1 cc. protected rabbits from 1000 to 10,000 times the M. L. D. of four virulent strains, it did not protect from 10 M. L. D.'s of a fifth strain, otherwise indistinguishable from the other four. Bensagon and Griffon,<sup>12</sup> Kindborg,<sup>13</sup> and Roemer<sup>14</sup> have also shown that a given serum differs markedly in its activity toward various strains of pneumococci, both in its agglutinating and protective power.

Neufeld and Haendel<sup>15</sup> have since shown that pneumococci can be subdivided into several groups, according to their reactions to immune sera, and their work has been confirmed by Cole and Dochez.<sup>16</sup> While all the strains in a given group, A, are about equally influenced by the serum of an animal immunized to one member of that group, a strain belonging to another group, B, will not be affected by this (group A) serum. That the failure of some to demonstrate protective power in postcritical serum may be due to such differences in the strain of organism used, is supported by the work of Dochez,<sup>17</sup> who has recently reported studies on 14 patients. Of ten cases in which an homologous organism was used, i. e., one cultivated from the patient whose serum was being studied, nine possessed sera which showed a definite, though often slight, protective power. Of four sera tested with a stock culture, three showed no protective power whatever, and the fourth gave only a very feeble protection.

Previous attempts to demonstrate the nature of the immune bodies which confer this protection have led to contradictory results. The immunity to the pneumococcus which develops naturally in man after pneumonia is at best but slight, and of short duration. Because of the much higher degree of immunity that can be produced experimentally in animals, study of their sera has led to more definite results, and has suggested what may be looked for in human serum. Without going into detail, a review of the extensive literature on the subject<sup>18</sup> shows that the only antibodies which have been constantly demonstrated in significant quantity are substances which promote phagocytosis.

The importance of phagocytosis in immunity to the pneumococcus was first definitely shown by Issaef.<sup>19</sup> He injected virulent pneumococcus cultures subcutaneously in normal and immunized rabbits. In the former he found that the organisms multiplied without restriction, leading to a septicæmia and to death of the animal. In the immunized rabbits, on the contrary, the organisms were ingested by leucocytes within six to ten hours; after 24 hours all the organisms had disappeared, and the animals recovered.

Mennes<sup>20</sup> first studied the action of immune serum and

leucocytes on pneumococci in the test tube, using the method employed by Denys and Leclef<sup>21</sup> for streptococci. He found that, as in the animal body, virulent pneumococci were not phagocytized at all in normal serum, but were rapidly ingested and destroyed in immune serum. He found that the leucocytes of the immune animal, if washed free from the serum, were no more active than those of a normal animal. He did not find any direct bactericidal or antitoxic action on the part of the serum, and hence attributed the immunity to this acquired power of the serum to cause phagocytosis of virulent organisms.

His conclusions have been confirmed by Huber,<sup>22</sup> and by the extensive researches of Neufeld<sup>23</sup> and his co-workers. Neufeld further showed that the serum acts, not by stimulating the leucocytes, but by altering the microorganisms so as to make them susceptible to phagocytosis by normal leucocytes. Hence he gave to these antibodies the name bacteriotropines. They differ from the opsonines of normal serum in being thermostabile (60° C.). Since the bacteriotropine content of an immune serum, measured by the dilution method, runs closely parallel with its power of protecting animals, Neufeld attributes the immunity largely, if not entirely, to these substances. There can be little doubt that they play the leading rôle in the immunity of the horse and rabbit to the pneumococcus, but conclusions based on the properties of the serum of immune animals cannot be applied without further study to man.

The numerous early efforts to demonstrate specific bactericidal substances in significant quantities in human serum were unsuccessful. More recently Much<sup>24</sup> and Dold<sup>25</sup> have shown that normal human serum, and, to a much greater degree, citrated plasma (free from leucocytes), have a definite inhibitory action, and often a slight bactericidal action on virulent pneumococci. This activity is not present in the plasma of susceptible animals like the mouse, the rabbit, and the horse. To this Neufeld and Dold ascribe that degree of natural immunity which is possessed by man to virulent pneumococci, and they attribute to it the slight protective power for mice exerted by normal human serum.

I have repeated Dold's experiments with several specimens of normal human and rabbit serum and plasma, and with the serum and plasma of four patients convalescent from pneumonia (Cases VII, VIII, XII and XIII). The results were quite in accord with those of Dold. A reduction in the number of colonies in human plasma could usually be demonstrated, but this activity was not perceptibly increased in pneumonic plasma; nor was it more marked for the homologous strain of pneumococcus than for an heterologous strain. This direct bactericidal activity of the serum can certainly be a factor of only secondary importance in the immunity developed at the crisis.

Most writers have attributed the immunity developing in man to increased phagocytic activity. Attempts to demonstrate such activity have been limited largely to determinations of the opsonic index by the Wright method (e. g., Rosenow,<sup>26</sup> Wolfe,<sup>27</sup> Boni,<sup>28</sup> Tunncliffe,<sup>29</sup> etc.). These observers



agree for the most part in finding a low opsonic index early in the disease, with a slight rise at the crisis; whereas, in unfavorable cases, there is a fall in the opsonic index before death. Even if we admit that the method is accurate enough to yield reliable results, the significance of such a rise in index is questionable. In such index determinations one must use a non-virulent or feebly virulent strain which is phagocytal in normal human serum. The organisms isolated from patients with pneumonia are almost invariably virulent and resistant to phagocytosis. This is true of strains cultivated from the sputum (Luetscher<sup>7</sup>), as well as from the blood (Rosenow,<sup>22</sup> etc.). A slight increase in the power of phagocytizing avirulent organisms would, therefore, be of no evident benefit to the patient, unless, with this, there appeared the power of phagocytizing virulent strains, such as that with which the patient is infected. As reported by the majority of observers, the serum of patients at the crisis is no more active than is normal serum in causing phagocytosis of such virulent strains (Rosenow,<sup>22</sup> Strouse,<sup>19</sup> Luetscher<sup>7</sup>).

Because of the similarity in the action of human postcritical serum and immune animal serum in protecting mice, Neufeld<sup>7</sup> thinks that the same antibodies are active in each. The crisis in man he explains as due to the appearance of antibodies (chiefly tropines) in the blood. The abruptness of the crisis he attributes to the fact that tropines are entirely inactive until they reach a certain *concentration* in the serum. They then suddenly become active, causing a rapid ingestion and destruction of all the hitherto non-phagocytal organisms. However, Neufeld does not offer any direct evidence proving that the active substances present in postcritical sera are tropines.

Foa<sup>23</sup> alone has reported that the serum of patients after crisis may cause phagocytosis of virulent organisms, not phagocytal in normal human serum. He found that serum heated at 56° C. was as active as fresh serum. He does not give his technic in detail further than that he followed Neufeld's method of using guinea-pig exudate leucocytes, and that he incubated the mixtures 45 minutes. The cultures he describes as "virulent," but the source of them is not stated. He gives no details as to the patients studied, nor does he expressly state that more than one individual case was tested.

Boettcher<sup>9</sup> has reported finding tropic activity in (heated) convalescent sera. Though she states that the cultures used were virulent strains obtained by blood cultures from patients with pneumonia, they could not have been highly virulent at the time the experiments were carried out, since they were phagocytal in normal serum. This increased activity of postcritical serum was therefore simply an increased power of ingesting a (relatively) avirulent phagocytal strain, and the significance of it is open to the same doubt as the reported increase in opsonic index, already described.

Boni<sup>24</sup> also reported finding increased phagocytic activity in heated serum at the crisis, as compared with normal heated serum. He describes the increase in heated serum (tropines) as more specific (as compared with staphylococci), but less

marked than that in active serum (opsonines, as well as tropines). He also used phagocytal organisms, and his results are open to the same criticism as are those of Boettcher, for this reason.

Strouse<sup>19</sup> alone reports the use of homologous strains as well as stock cultures. He obtained entirely negative results with virulent non-phagocytal strains, and this was perhaps due to the fact that he used the sera in too high dilution (1 in 10 to 1 in 1000).

Rosenow<sup>22</sup> found that the bactericidal power of pneumonic defibrinated blood (for phagocytal strains) was greater than that of normal blood. This he found was due to phagocytosis. The increased activity bore no relation to the crisis, and was no more marked for the homologous than for an heterologous strain, but it was roughly proportional to the leucocytosis, and was attributed by him to a non-specific increase in the activity of the pneumonic leucocytes.

Tunnicliff<sup>25</sup> found at the crisis, by the plate method, an increase in the pneumococidal power of the blood (serum and leucocytes) for avirulent strains only, which was roughly parallel with the rise in opsonic index. Eggers<sup>26</sup> found a similar increase for stock cultures of "moderate virulence." This he attributed to phagocytosis, but did not exclude the possibility of its being due in part to agglutination.

Because of these contradictory results it seemed desirable carefully to study the sera of a selected series of cases. The special object of the work was to determine the constancy with which antibodies appear at the crisis, and if possible to demonstrate their nature. It seemed probable that the failure of previous investigations was due to some common fundamental error in the methods employed. The work of Neufeld and Haendel suggested that this error was probably to be found in a difference between the strain of the organism used in the tests and that with which the patient was infected. Therefore, in all except one of the following series of cases the homologous virulent strain was employed. The activity of the serum of the patient after crisis (or lysis) was compared with that of normal serum, and in the last two cases with that of the same patient before the crisis, both as to its power passively to protect mice, and its power to promote phagocytosis in the test tube.

#### TECHNIC.

The cultures were isolated from the sputum of the patient as early as possible in the disease, in every instance before the temperature began to fall. The method used was that employed by Luetscher.<sup>7</sup> A single specimen of sputum, raised after a paroxysm of coughing, was expectorated into a sterile Petri dish, and immediately washed thoroughly three to eight times in sterile broth. A small particle of the washed sputum, or a few loops of broth from the last washing, were smeared with a sterile, bent glass rod over the surface of several human blood agar plates, and the latter incubated 24 hours. If the sputum was tenacious enough to permit thorough washing, practically pure cultures were easily obtained, containing at most four or five contaminating colonies on each plate. If

\* Personal communication.

not tenacious enough to permit mouth contaminations to be washed entirely off, pure cultures could not be obtained. But if the great majority of the colonies (at least 80 per cent) were typical pneumococcus colonies, the culture was considered satisfactory, subcultures from several colonies were made, and their cultural reactions tested. Only typical strains were used. If culturally a typical pneumococcus was obtained, its phagocytability in normal human serum was determined, and, as a rule, its virulence for mice roughly tested. If non-phagocytatable, and of such virulence that the M. L. D. for mice did not exceed 0.0002 cc. of a 24-hour serum-meat-infusion-broth culture, it was used without animal passage. This method of isolation was chosen in preference to the much easier one of animal inoculation in order to avoid a possible increase in virulence of the strain as a result of the animal passage. It was felt that the virulence of the strain isolated by plating would represent more accurately the virulence of the organism as it existed in the body of the patient than if animal inoculation were resorted to. A possible increase in virulence might conceivably hide a moderate degree of protective power in the serum. However, no comparative studies of the virulence of sputum strains isolated by the two methods were made.

From their isolation until used the strains were cultivated on rich, moist, human blood agar. Transfers were made at intervals of 1 to 3 or 4 days, care being taken to avoid desiccation. The results of these experiments indicated that, in the course of a few days to a few weeks, no change in the phagocytability of the organism occurred, nor was there any appreciable loss of virulence. That any loss of virulence can occur in the single generation on blood agar required for isolation, is scarcely conceivable.

In three cases growth was also obtained in blood cultures. In two cases comparative tests of the virulence of blood and sputum strains, isolated at the same time, were made. In one case the blood strain, tested, however, 15 days after isolation, was distinctly less virulent than the sputum strain, tested 35 days after isolation, and again 52 days after isolation. In the third case both strains tested immediately were of equal and of very high virulence. The reliability of such sputum isolations is supported by the fact that in both cases the strains from the blood and sputum were identical in their serum reactions.

The blood was obtained by aspiration from the median basilic vein. The sterile serum was pipetted off after contraction of the clot, and stored on ice in the dark, without inactivation or the addition of a preservative. In the earlier cases but one specimen, taken one or two days after the crisis was examined. In later cases, where possible, several specimens, taken at intervals before and after crisis were tested.

In the first eleven cases the technic followed in the serum protection experiments was that described by Neufeld.<sup>7</sup> Each of a series of mice were injected into the peritoneal cavity with 0.2 cc. of patient's serum, a second series of control animals receiving the same quantity of normal serum. Three hours later all received intraperitoneal injections of a 24-hour

serum-meat-infusion-broth culture of the homologous strain of pneumococci. The doses varied from 0.02 cc. to 0.000002 cc. in a volume of 0.2 cc. The mice were kept under observation for ten days or two weeks. As a rule, however, more definite, clear-cut results are obtained if the period of observation is shortened arbitrarily to four days, as recommended by Neufeld.<sup>7</sup> If the cultures are of the usual high virulence the control animals (receiving normal serum) die, as a rule, within 48 hours, and almost invariably they show a general septicaemia. A considerable proportion of the protected animals will outlive the controls, but will die later, after four to fifteen days. Cultures from the blood and peritoneum of such animals are almost invariably sterile. In some cases large hæmorrhages in the serous cavities were found, as described by Sprunt and Luetscher,<sup>8</sup> due to toxic degenerative changes in the elastic tissue of the large arteries. The animals in these cases seem to have overcome the infection and killed off the invading organisms, only to succumb to the late effects of the liberated toxins. While death is not prevented, the prolongation of life, and the sterile cultures after death, may be accepted as definite indications of some degree of protective power on the part of the serum. At best, the test is but a comparative quantitative one. Neufeld and others have shown that normal serum as used here often protects mice slightly but definitely from highly virulent cultures. In all cases autopsies were performed and the presence or absence of organisms in the blood and the peritoneum determined by smears, cultures, or by both.

In the last four cases Dochez's method was followed.<sup>10</sup> The serum (0.2 cc.) and each culture dilution (also 0.2 cc. in volume) were mixed in the test tube and after standing for about an hour the whole was injected intraperitoneally. This is undoubtedly better than the Neufeld method, and failure to use it may explain some of the early negative results.

#### PHAGOCYTOSIS TESTS.

The phagocytosis tests were carried out in every case with the virulent strain isolated during the acute stage from the sputum (or blood) of the patient whose serum was tested. With but two exceptions, discussed in detail later, they were not phagocytatable in fresh normal human serum, under the conditions of the experiment. In every case several heterologous strains were also used, for the purpose of comparison. In particular, each serum showing any action on its homologous organism was also tested with the strain from every previous patient whose serum had shown any phagocytic activity. Fairly thick emulsions of the organism were made from 24-hour blood agar slants by rubbing up a loop of the growth in two or three drops of salt solution. The sera were used both in fresh condition and after inactivation for 30 minutes at 56° to 60° C. In a few instances the sera were also diluted 1 in 3, 1 in 10, 1 in 30, and 1 in 100. But experience soon showed that the activity was so slight that it usually disappeared entirely in a dilution of even 1 in 3. The leucocyte suspension was obtained either by defibrinating a few cubic centimeters of normal human blood or by mixing it in 1.5 per

cent sodium citrate solution, and washing three times in 0.85 per cent salt solution. The upper layers (the leucocytic "cream") were pipetted off, and thoroughly mixed, to insure a uniform suspension of leucocytes.

For the test equal volumes of serum, bacterial suspension, and leucocyte suspension were mixed and incubated at 37° C. in capillary pipettes, as in Wright's method.

After incubation smears of the mixtures were made by pulling a drop over the surface of one slide with the edge of a second narrower slide. The smears were fixed for two or three minutes in absolute methyl alcohol and stained for several minutes in methylene blue.

In every case, in addition to the preparations containing fresh, and those containing heated patient's serum, control preparations were made, some containing fresh normal serum, some heated normal serum, and some salt solution alone. In examining the smears counts were not made. Only gross differences easily recognizable after a rapid general survey of the preparation were regarded as of any significance. The degree of phagocytosis was described as absent (0), definite (+), strong (++), and maximal (+++). Unless the control preparations, containing normal serum, showed either a complete absence of phagocytosis, or at most a minimal degree of it (perhaps 10 or 20 pair in 50 leucocytes), phagocytosis in the test preparations was not regarded as significant. Some regard must be paid, however, to the time of incubation in order to get clear cut results. As a rule, the best preparations were obtained after 30 minutes incubation. If these were negative similar mixtures were incubated for one and two hours, but rarely was anything gained by the longer incubation. On the contrary, in several cases where, after 30 minutes incubation, the normal serum controls showed no phagocytosis and the postcritical serum strong phagocytosis, after two hours incubation the difference was much less definite, owing to a certain amount of spontaneous phagocytosis taking place in the controls. In other cases no phagocytosis took place, no matter how prolonged the incubation. A further drawback to prolonged incubation is the fact that not infrequently quite a marked degree of intracellular digestion of the organisms takes place, making them stain very poorly. Not infrequently, too, the leucocytes themselves showed signs of degeneration as if injured by the prolonged contact with the organisms. The activity of the leucocytes was always demonstrated by control mixtures containing a strain known to be easily phagocytizable in normal serum.

This method was chosen in preference to the Neufeld method, in which guinea-pig leucocytes are used, because of the possible advantage of using homologous leucocytes, as Ungermann<sup>22</sup> has shown that under certain conditions sera may exert a bacteriotropic action only in the presence of homologous leucocytes.

In every instance the experiments were repeated once or twice on subsequent days with different specimens of normal serum and leucocytes to insure that the results were not accidental.

While this method gave satisfactory results as a routine

procedure, it proved not to be delicate enough to demonstrate tropic activity in all cases. As above described, the mixture contains one volume of serum diluted with two parts of salt solution (bacterial and leucocyte suspension). As the sera which were active under such conditions lost their activity when diluted 1 in 3 (so that the actual serum concentration in the mixture was 1 in 9), it was felt that the method would prove more accurate if serum were employed instead of salt solution as the suspending medium.

In the one case in which there was an opportunity to test this modification, a positive result was obtained, whereas the regular method above described gave a negative result. Instead of suspending the culture in salt solution, it was suspended in a drop of postcritical serum, a control suspension being made in normal serum. Instead of using washed leucocytes, a suspension was prepared directly from the defibrinated blood of the patient and of a normal individual. This would permit sensitization of the cocci to take place in concentrated serum before being exposed to the action of the leucocytes, and would take advantage of any extra activity the latter might show when suspended in their own serum, as compared with a salt solution suspension. Equal parts of leucocyte suspension in serum and culture suspension in postcritical serum gave positive results, whereas normal leucocyte suspension and culture suspension in normal serum showed no trace of phagocytosis.

A further possible cause of failure might be the presence of inhibiting substances in the concentrated serum, as suggested by Neufeld. In negative cases, therefore, the organisms should also be digested in the serum and then washed before leucocytes are added.

Failure to use these modifications may be the cause of some of the earlier negative results.

#### REPORT OF CASES.

CASE I.—L. F., colored female, aged 13, was admitted to the hospital May 19, 1911, on the second day of the disease, with signs of consolidation of the right upper lobe, later extending to the middle and lower lobes as well. Blood culture on the fifth day gave a growth of pneumococcus. The strain used was plated from the sputum on the eighth day. The temperature fell by very protracted lysis from 102° on the sixth day to 100° F. on the sixteenth day. There was a slight elevation of temperature, from 99° to 100° F., for the following four weeks, with signs of delayed resolution. The patient was discharged August 2, with normal temperature and physical signs. The serum used was obtained May 28 (the eleventh day) and June 1 (the fifteenth day), both during lysis.

No.	Culture Dose.	Result.			
		May 28st.		June 1st.	
		Series A. Nor- mal Serum.	Series B. Ser- um 17th Day.	Series C. Nor- mal Serum.	Series D. Ser- um 15th Day.
1	5,000,000 pair.	+ 27 hours.	— " "	— 4 " "	Lived.
2	20,000,000 pair.	+ 24 hours.	— " "	+ 24 hours.	+ 5 days.
3	80,000,000 pair.	+ 30 hours.	— " "	Cult. +.	Lived.
4	320,000,000 pair.	— " "	— " "	Cult. 0.	— " "



In this one series a counted suspension of organisms from a blood agar slant was used. There was definite protective power shown by the serum obtained on the eleventh day, and also by that obtained on the fifteenth day.

The phagocytic activity of the serum was not tested.

CASE II.—R. G., colored male, 23 years old, entered the hospital November 27, 1911, on the third day of the disease, with signs of consolidation of the right middle lobe. The pneumococcus was plated from the sputum November 28. The temperature fell by lysis on the eighth to the eleventh days. The case was clinically a mild one. The serum was obtained December 4, on the tenth day, two days after the temperature began to fall, but two days before it reached normal.

#### RESULT OF TEST DECEMBER 4, 1911.

Dose of Culture.	Series A. No Serum.	Series B. Serum, Dec. 4.
0.1 cc.	—	—
0.01 cc.	—	—
0.001 cc.	—	—
0.0001 cc.	—	—
0.00001 cc.	—	—
0.000001 cc.	—	—
	+ 48 hours.	

There was no evidence of protective power, but rather an increased susceptibility to the culture, on the part of the treated mice. This probably is due to the use of serum obtained during the febrile stage. Washbourn<sup>24</sup> found that serum (blister fluid) of patients, during the acute stage of the disease, in six out of seven cases, distinctly increased the susceptibility of rabbits to a virulent pneumococcus culture.

The phagocytic activity of the serum was not tested.

CASE III.—C. W., colored male, 23 years old, was admitted to the hospital February 24, 1912, on the third day of the disease, with signs of consolidation of the right upper, middle, and lower lobes. Blood culture gave no growth. The temperature fell by protracted crisis on the ninth and tenth days. The serum was obtained ten days after the crisis. A stock culture of very high virulence was used, instead of an homologous strain. This may explain the complete failure to demonstrate any protective power.

The phagocytic activity of the serum was not tested.

#### RESULT MARCH 11, 1912.

No.	Culture Dose.	Series A. Normal Serum.	Series B. Normal Serum, March 11.
1	0.0000001 cc.	+ 2 days.	—
2	0.0000001 cc.	+ 2 days.	+ 2 days.
3	0.0000001 cc.	—	+ 2 days.
4	0.0000001 cc.	—	+ 2 days.
5	0.0000001 cc.	—	+ 2 days.
6	0.0000001 cc.	—	+ 2 days.
7	0.0000001 cc.	—	+ 2 days.
8	0.0000001 cc.	—	+ 2 days.
9	0.0000001 cc.	—	+ 2 days.
10	0.0000001 cc.	—	+ 2 days.
11	0.0000001 cc.	—	+ 2 days.
12	0.0000001 cc.	—	+ 2 days.
13	0.0000001 cc.	—	+ 2 days.
14	0.0000001 cc.	—	+ 2 days.
15	0.0000001 cc.	—	+ 2 days.
16	0.0000001 cc.	—	+ 2 days.
17	0.0000001 cc.	—	+ 2 days.
18	0.0000001 cc.	—	+ 2 days.
19	0.0000001 cc.	—	+ 2 days.
20	0.0000001 cc.	—	+ 2 days.
21	0.0000001 cc.	—	+ 2 days.
22	0.0000001 cc.	—	+ 2 days.
23	0.0000001 cc.	—	+ 2 days.
24	0.0000001 cc.	—	+ 2 days.
25	0.0000001 cc.	—	+ 2 days.
26	0.0000001 cc.	—	+ 2 days.
27	0.0000001 cc.	—	+ 2 days.
28	0.0000001 cc.	—	+ 2 days.
29	0.0000001 cc.	—	+ 2 days.
30	0.0000001 cc.	—	+ 2 days.
31	0.0000001 cc.	—	+ 2 days.
32	0.0000001 cc.	—	+ 2 days.
33	0.0000001 cc.	—	+ 2 days.
34	0.0000001 cc.	—	+ 2 days.
35	0.0000001 cc.	—	+ 2 days.
36	0.0000001 cc.	—	+ 2 days.
37	0.0000001 cc.	—	+ 2 days.
38	0.0000001 cc.	—	+ 2 days.
39	0.0000001 cc.	—	+ 2 days.
40	0.0000001 cc.	—	+ 2 days.
41	0.0000001 cc.	—	+ 2 days.
42	0.0000001 cc.	—	+ 2 days.
43	0.0000001 cc.	—	+ 2 days.
44	0.0000001 cc.	—	+ 2 days.
45	0.0000001 cc.	—	+ 2 days.
46	0.0000001 cc.	—	+ 2 days.
47	0.0000001 cc.	—	+ 2 days.
48	0.0000001 cc.	—	+ 2 days.
49	0.0000001 cc.	—	+ 2 days.
50	0.0000001 cc.	—	+ 2 days.
51	0.0000001 cc.	—	+ 2 days.
52	0.0000001 cc.	—	+ 2 days.
53	0.0000001 cc.	—	+ 2 days.
54	0.0000001 cc.	—	+ 2 days.
55	0.0000001 cc.	—	+ 2 days.
56	0.0000001 cc.	—	+ 2 days.
57	0.0000001 cc.	—	+ 2 days.
58	0.0000001 cc.	—	+ 2 days.
59	0.0000001 cc.	—	+ 2 days.
60	0.0000001 cc.	—	+ 2 days.
61	0.0000001 cc.	—	+ 2 days.
62	0.0000001 cc.	—	+ 2 days.
63	0.0000001 cc.	—	+ 2 days.
64	0.0000001 cc.	—	+ 2 days.
65	0.0000001 cc.	—	+ 2 days.
66	0.0000001 cc.	—	+ 2 days.
67	0.0000001 cc.	—	+ 2 days.
68	0.0000001 cc.	—	+ 2 days.
69	0.0000001 cc.	—	+ 2 days.
70	0.0000001 cc.	—	+ 2 days.
71	0.0000001 cc.	—	+ 2 days.
72	0.0000001 cc.	—	+ 2 days.
73	0.0000001 cc.	—	+ 2 days.
74	0.0000001 cc.	—	+ 2 days.
75	0.0000001 cc.	—	+ 2 days.
76	0.0000001 cc.	—	+ 2 days.
77	0.0000001 cc.	—	+ 2 days.
78	0.0000001 cc.	—	+ 2 days.
79	0.0000001 cc.	—	+ 2 days.
80	0.0000001 cc.	—	+ 2 days.
81	0.0000001 cc.	—	+ 2 days.
82	0.0000001 cc.	—	+ 2 days.
83	0.0000001 cc.	—	+ 2 days.
84	0.0000001 cc.	—	+ 2 days.
85	0.0000001 cc.	—	+ 2 days.
86	0.0000001 cc.	—	+ 2 days.
87	0.0000001 cc.	—	+ 2 days.
88	0.0000001 cc.	—	+ 2 days.
89	0.0000001 cc.	—	+ 2 days.
90	0.0000001 cc.	—	+ 2 days.
91	0.0000001 cc.	—	+ 2 days.
92	0.0000001 cc.	—	+ 2 days.
93	0.0000001 cc.	—	+ 2 days.
94	0.0000001 cc.	—	+ 2 days.
95	0.0000001 cc.	—	+ 2 days.
96	0.0000001 cc.	—	+ 2 days.
97	0.0000001 cc.	—	+ 2 days.
98	0.0000001 cc.	—	+ 2 days.
99	0.0000001 cc.	—	+ 2 days.
100	0.0000001 cc.	—	+ 2 days.

CASE IV.—F. C., white male, 23 years old, was admitted April 8, 1912, on the second day of the disease, with signs of consolidation

#### RESULT APRIL 22, 1912.

Culture Dose.	Series A. Normal Serum.	Series B. Normal Serum, April 16.
0.2 cc.	—	—
0.02 cc.	—	—
0.002 cc.	—	—
0.0002 cc.	—	—
0.00002 cc.	—	—
	+ 2 days.	+ 2 days.

of the right lower lobe. Blood cultures were sterile. The culture used was plated from the sputum on the third day of the disease. The temperature fell by crisis on (April 13) the seventh day. The serum was obtained three days after the crisis.

There was no protective power whatever. The doses used were a little too large.

The phagocytic activity of the serum was not tested.

CASE V.—C. P., white male, 19 years old, was admitted May 5, 1912, on the second day of the disease, with signs of consolidation of the right upper and left lower lobes. Blood culture showed no growth. The culture used was plated from the sputum on the second day. The temperature fell to normal by protracted crisis on the tenth and eleventh days. Serum was obtained May 14, the day after crisis.

#### RESULT MAY 14, 1912.

No.	Culture Dose.	Series A. Control Serum.	Series B. P—Serum of May 14.
1	0.2 cc.	— 24 hours.	+ 48 hours.
2	0.02 cc.	+ 24 hours.	+ 48 hours.
3	0.002 cc.	Lived.	Lived.
4	0.0002 cc.	+ 48 hours.	Lived.
5	0.00002 cc.	+ 48 hours.	Lived.

There was definite protection from ten and from a hundred times the dose fatal for control mice. The survival of one control mouse, which received a larger dose than two of the others which died, illustrates an irregularity not infrequently met with, and probably referable to an individual peculiarity of this mouse.

#### PHAGOCYTOSIS TEST MAY 16.

- (1) Washed normal leucocytes + P— culture suspension + normal serum. Phagocytosis 0.
- (2) Leucocytes + P— culture + P— serum (May 14). Phagocytosis ++ (strong).

The serum thus showed definite phagocytic activity as compared with normal serum.

CASE VI.—A. H., white male, aged 19 years, was admitted December 7, 1912, on the third day of the disease, with consolidation of the right middle and lower lobes. Blood culture gave no growth. The culture used was plated from the sputum on the fourth day. The temperature fell by crisis very abruptly on the seventh day (December 11). The serum was obtained December 13, two days after crisis.

#### RESULT DECEMBER 14, 1912.

No.	Culture Dose.	Series A. Control Serum.	Series B. H—Serum of December 13.
1	0.02 cc.	— 18 hours.	+ 18 hours.
2	0.002 cc.	— 2 days.	+ 2 days.
3	0.0002 cc.	— 2 days.	+ 2 days.
4	0.00002 cc.	— 2 days.	+ 2 days.
5	0.000002 cc.	— 2 days.	+ 2 days.

There was not the slightest evidence of protection. Phagocytosis tests were also negative.

- (1) Washed leucocytes + H— culture + normal serum = 0.
- (2) Washed leucocytes + H— culture + H— serum = almost 0.

The difference in the preparations was so slight as to be negligible.

CASE VII.—S. T., white male, aged 18 years, was admitted March 8, 1913, on the third day, with signs of consolidation of the right lower lobe. Blood culture on March 10 showed no growth. The culture used was plated from the sputum on the fourth day. The temperature fell by crisis on the seventh day (March 12) to 99° F.,

but continued slightly elevated (99° to 100° F.) for ten days. The serum was obtained March 13, two days after crisis.

## RESULT MARCH 13, 1913.

No.	Culture Dose.	Series A. Control Serum.	Series B. T— Serum.
1	0.2 cc.	+ 6 days (cult. positive).	+ 6 days.
2	0.02 cc.	Lived.	+ 4 days.
3	0.002 cc.	+ 3 days.	+ 6 days.
4	0.0002 cc.	+ 5 days.	Lived.
5	0.00002 cc.	+ 6 days.	+ 5 days.
6	0.000002 cc.	Lived.	+ 5 days.

No protective power was shown.

As the culture was of low virulence and killed slowly, the virulence was raised by passage through 8 mice, and the tests repeated, using the same specimen of serum.

## RESULT JUNE 16, 1913.

No.	Culture Dose.	Series A. Normal Serum.	Series B. T—Ser., March 13.
1	0.02 cc.	+ 24 hours.	+ 24 hours.
2	0.002 cc.	+ 48 hours.	+ 24 hours.
3	0.0002 cc.	+ 48 hours.	+ 24 hours.
4	0.00002 cc.	Lived.	+ 24 hours.
5	0.000002 cc.	Lived.	+ 24 hours.

A control mouse receiving T—'s serum without culture lived. In this series the sera were mixed with culture dilutions and the mixtures were injected into the mice. The patient's serum (which might conceivably have weakened in three months) not only offered no protection, but favored infection, as compared with the normal serum controls. This failure to show protection may be due to the fact that the serum was taken before the temperature had quite reached normal.

Phagocytosis tests were also negative. T—'s culture was not phagocytized at all by washed leucocytes, either in normal serum, or in T—'s serum of March 13.

CASE VIII.—F. P., colored male, 19 years old, was admitted March 11, 1913, on the fourth day, with consolidation of the left upper lobe. The pneumococcus was cultivated from the blood on the fifth day, about 5 colonies per cubic centimeter. The strain used was plated from the sputum on the fifth day. The temperature fell by crisis on the tenth day (March 17). There was a slight persistent post-critical elevation of temperature, with persisting signs of consolidation in the left upper lobe, which were regarded clinically as indicating delayed resolution. They subsided gradually after ten days. The serum used was obtained March 18, the day after crisis.

## RESULT MARCH 23, 1913.

No.	Culture Dose.	Series A. Normal Serum.	Series B. P— Serum, March 18.
1	0.02 cc.	+ 1 day culture +	+ 1 day culture +
2	0.002 cc.	+ 1 day culture +	+ 1 day culture +
3	0.0002 cc.	+ 2 days culture +	+ 2 days culture +
4	0.00002 cc.	+ 1 day culture +	+ 3 days culture sterile.
5	0.000002 cc.	+ 1 day culture +	+ 5 days culture sterile.

Some protection was shown. The mice Nos. 4 and 5, in Series B, outlived the controls, and overcame the infection, as shown by sterile cultures, whereas the controls all showed a septicaemia.

Phagocytosis tests were negative. The strain P— was not phagocytized by washed leucocytes, either in fresh normal serum, or in P—'s postcritical serum.

CASE IX.—L. T., colored female, 20 years of age, was admitted March 17, on the fifth day, with signs of consolidation of the right middle and lower lobes. Blood culture on admission gave no

growth. The culture was plated from the sputum on the fifth day. The temperature fell by protracted crisis on the sixth and seventh days. Serum was obtained on March 20, the day after crisis.

## RESULT APRIL 11, 1913.

No.	Culture Dose.	Series A. Normal Serum.	Series B. T— Serum, March 20.
1	0.02 cc.	+ 24 hours culture +	+ 24 hours culture +
2	0.002 cc.	+ 24 hours culture +	+ 48 hours culture +
3	0.0002 cc.	+ 24 hours culture +	+ 48 hours culture +
4	0.00002 cc.	+ 48 hours culture +	+ 3 days culture sterile.
5	0.000002 cc.	+ 48 hours culture +	+ 3 days culture sterile.

There is a slight degree of protective power shown in that two of the protected mice outlived the controls, and gave sterile cultures.

Phagocytosis tests were negative. The strain T— was not phagocytized by washed leucocytes, either in normal serum, or in T—'s postcritical serum.

CASE X.—J. A., colored male, aged 29, was admitted March 24, 1913, on the third day of the disease, with consolidation of the right upper lobe. Blood culture on admission gave no growth. The culture was plated from the sputum on the fourth day. The temperature fell by crisis on the fifth day (March 26). Serum was obtained March 27, the day after crisis.

## RESULT APRIL 11, 1913.

No.	Culture dose.	Series A. Normal Serum.	Series B. A— Serum, March 27.
1	0.02 cc.	+ 7 days.	+ 3 days culture 0.
2	0.002 cc.	+ 3 days culture +	+ 6 days.
3	0.0002 cc.	+ 4 days culture +	+ 1 day.
4	0.00002 cc.	+ 4 days culture +	+ 3 days culture 0.
5	0.000002 cc.	+ 4 days.	+ 3 days culture 0.

There was no evidence of protective power. Attempts to increase the virulence of the strain by passage through six mice were unsuccessful.

There was no demonstrable increase in phagocytic activity. The strain A— was not phagocytized at all by washed leucocytes, either in normal serum, or in A—'s postcritical serum.

CASE XI.—W. R., colored male, aged 27, was admitted March 7, 1913, on the fourth day of the disease, with consolidation of the right upper and middle lobes. The pneumococcus was cultivated from the blood on admission, one colony per cubic centimeter (strain R— blood). In addition a sputum strain was used, isolated by plating, on the fourth day. The temperature fell by lysis on the eighth to the tenth days. The serum was obtained March 14, the day after the temperature became normal.

## RESULT MARCH 22, 1913, USING STRAIN R— BLOOD.

No.	Culture Dose.	Series A. Normal Serum.	Series B. R— Serum, 11th day.
1	0.02 cc.	+ 2 days culture 0.	+ 10 days.
2	0.002 cc.	+ 8 days culture 0.	+ 2 days culture +
3	0.0002 cc.	+ 6 days culture 0.	Lived.
4	0.00002 cc.	+ 5 days culture 0.	+ 5 days.
5	0.000002 cc.	+ 3 days	

The protected animals on the average outlived the controls. But the virulence of the culture (after two weeks cultivation on blood agar) was too low to give definite results.

## RESULT APRIL 10, 1913.

No.	Culture Dose.	Series A. Normal Serum.	Series B. R— Serum.	No Serum.
1	0.02 cc.	+ 1 day culture +	+ 1 day culture 0.	24 hours.
2	0.002 cc.	+ 1 day culture +	+ 1 day culture 0.	24 hours.
3	0.0002 cc.	+ 1 day culture +	Lived.	24 hours.
4	0.00002 cc.	+ 6 days culture 0.	+ 2 days culture 0.*	+ 48 hours.
5	0.000002 cc.	Lived.	+ 2 days culture 0.	24 hours.

\* This mouse died of a large intrapleural hemorrhage.

Second Test: Here the strain isolated from the sputum was used. It had been grown for five weeks on blood agar, without passage through animals.

This series showed well-marked protection in the survival of the treated mice for a considerably longer period than the controls, and in their yielding sterile cultures, in contrast with the septiciemias in the controls.

The phagocytosis tests will be described in connection with Case XII.

CASE XII.—C. S., colored male, aged 34, was admitted to the hospital March 18, 1913, on the sixth day, with signs of consolidation of the left lower lobe. Blood culture on March 20 was sterile. The culture used was plated from the sputum on the seventh day. The temperature fell by crisis on the tenth day, though there was a persistent elevation of temperature to about 100° F. for two weeks. This was associated with an encapsulated effusion (X-ray) in the left lower chest, which finally was absorbed spontaneously, and the patient was discharged well April 14. The serum was obtained March 22, the day of crisis.

#### RESULT APRIL 16, 1913.

No.	Culture Dose.	Series A. Normal Serum.	Series B. S—Serum, 10th day.
1	0.02 cc.	+ 2 days.	Lived.
2	0.002 cc.	+ 2 days.	Lived.
3	0.002 cc.	+ 2 days.	Lived.
4	0.0002 cc.	+ 1 day.	+ 6 days.
5	0.00002 cc.	Lived.	+ 7 days.

There was definite and fairly strong protective power demonstrated.

#### PHAGOCYTOSIS TESTS WITH SERA OF CASES XI AND XII.

No.	Leucocytes.	Cultures Used.	Serum Used.	Degree of Phagocytosis.
1	Washed leucocytes	R—blood +	Normal serum.	0
2	Washed leucocytes	R—blood +	R—serum (fresh).	++
3	Washed leucocytes	R—sputum +	Normal serum.	0
4	Washed leucocytes	R—sputum +	R—serum (fresh).	+++
5	Washed leucocytes	R—sputum +	R—serum (heated to 56° C.).	++
6	Washed leucocytes	R—sputum +	R—serum (diluted 1 in 3).	Almost 0.
7	Washed leucocytes	R—sputum +	R—serum (diluted 1 in 3 + normal serum).	Almost 0.
8	Washed leucocytes	R—sputum +	R—serum (26 days old).	++
9	Washed leucocytes	R—sputum, after passage through a mouse.	R—serum.	+++
10	Washed leucocytes	S—sputum +	R—serum.	0
11	Washed leucocytes	P—sputum +	R—serum.	0
12	Washed leucocytes	T—sputum +	R—serum.	0
13	Washed leucocytes	A—sputum +	R—serum.	0
14	Washed leucocytes	S—sputum +	Normal serum.	0
15	Washed leucocytes	S—sputum +	S—serum (fresh).	+++
16	Washed leucocytes	S—sputum +	S—serum (heated to 56° C.).	++
17	Washed leucocytes	S—sputum +	S—serum (diluted 1 in 3).	+
18	Washed leucocytes	R—sputum +	S—serum.	+
19	Washed leucocytes	T—sputum +	S—serum.	+
20	Washed leucocytes	A—sputum +	S—serum.	0
21	Washed leucocytes	S—sputum +	S—serum (20 days old).	++
22	Washed leucocytes	S—sputum +	S—serum (32 days old).	Almost 0.
23	Washed leucocytes	R—sputum +	R—serum (40 days old).	++
24	Washed leucocytes	R—sputum +	R—serum (50 days old).	+

The results of several series of tests are combined in the table above. They show that the postcritical serum of each of these two patients caused active phagocytosis of the homologous virulent strain, which, in each case, was not phagocytized in normal human serum. Neither serum caused any phagocytosis whatever of the strain isolated from the other patient, nor of several other heterologous strains. These two strains,

therefore, differed sharply in their serum reactions, as tested in vitro, and presumably might fall into different groups, though they were practically identical culturally. To determine whether the sera showed the same specificity in strain in their power of protecting mice, as in their phagocytic activity in vitro, the following crossed protection tests were carried out, the same specimens of serum being used as in earlier tests. The cultures used were R—sputum, and S—sputum, after it had been passed through one mouse.

#### RESULT APRIL 26, 1913.

No.	Culture R—, Culture Dose.	Series A. Normal Serum.	Series B. R—Serum.	Series C. S—Serum.
1	0.02 cc.	+ 1 day culture +	— 4 days culture 0.	+ 1 day cult. +
2	0.002 cc.	+ 1 day culture +	Lived.	+ 2 d's cult. +
3	0.0002 cc.	+ 2 days culture +	Lived.	+ 2 d's cult. +
4	0.00002 cc.	+ 2 days culture +	Lived.	+ 2 d's cult. +
5	0.000002 cc.	Lived.	Lived.	+ 1 day cult. +

No.	Culture S—, Culture Dose.	Series D. Normal Serum.	Series E. R—Serum.	Series F. S—Serum.
1	0.02 cc.	+ 2 days culture +	+ 2 days cult. 0.	Lived.
2	0.002 cc.	+ 3 days culture +	+ 2 days cult. +	+ 2 days cult. 0.
3	0.0002 cc.	+ 3 days culture +	+ 2 days cult. +	+ 2 days cult. 0.
4	0.00002 cc.	+ 3 days culture +	+ 2 days cult. +	Lived.
5	0.000002 cc.	+ 5 days culture +	+ 2 days cult. +	+ 2 days cult. 0.

These tests showed that the protective power for mice of these sera ran parallel with the phagocytic activity in the test tube. R—serum protected very well from the homologous strain, but did not at all from S—. S—'s serum, on the other hand, did not show the least protective power toward R—, but did protect definitely, though rather feebly, from the homologous strain, S—.

CASE XIII.—W. D., colored male, 17 years old, was admitted April 24, 1913, on the fifth day, with consolidation of the right lower lobe. Blood culture on admission was negative. The culture used was plated from the sputum April 24. The temperature fell by crisis on the sixth day. Serum was obtained May 3, ten days after crisis.

#### RESULT MAY 16, 1913.

No.	Culture Dose.	Series A. Normal Serum.	Series B. D—Serum.
1	0.02 cc.	+ 2 days culture +	Lived.
2	0.002 cc.	+ 3 days culture +	+ 4 days culture 0.
3	0.0002 cc.	+ 1 day culture 0.	Lived.
4	0.00002 cc.	+ 2 days culture 0.	Lived.
5	0.000002 cc.	+ 2 days culture 0.	+ 1 day culture 0.

There was well marked protective power manifested.

Phagocytosis tests May 3, 1913. As the ordinary method gave negative results, special methods, already described, were used.

No.	Leucocytes.	Culture Strain Suspended In.	Serum.	Result Degree of Phagocytosis.
1	Normal blood.	D— in normal serum.	Normal.	0
2	D— blood.	D— in D— serum.	D—.	+++
3	Normal blood.	D— in D— serum.	D—.	++
4	Normal blood.	D— in salt solution.	D—.	0
5	D— blood.	R— in salt solution.	D—.	0
6	D— blood.	S— in salt solution.	D—.	0
7	D— blood.	P— in salt solution.	D—.	0
8	D— blood.	N— in salt solution.	D—.	0

By suspending the cocci directly in serum and using defibrinated blood in place of washed leucocytes, marked phagocytosis of D—



strain was demonstrated in his own serum; but none whatever in normal serum. The patient's leucocytes seemed to be slightly more active than normal leucocytes; but the essential factor in this activity was in the serum. The serum had no effect on four heterologous strains treated, three of which had been phagocytizable in the postcritical serum of the patient from whom they were cultivated.

CASE XIV.—R. C., white male, aged 49, was admitted May 20, 1913, on the first day of the disease, later developing signs of consolidation of the left upper and lower lobes. Blood culture on the second day was sterile. The culture was plated from the sputum on the second day. It was of the streptococcus mucosus type. The temperature fell abruptly (pseudocrisis) on the fifth day, but rose again, and fell by lysis, to normal on May 30. Serum was obtained May 21, May 23, May 26 (during lysis), and May 31 (after complete lysis).

## RESULT MAY 27, 1913.

No.	Culture Dose	Series A. Normal Serum	Series B. C—, 5-26	Series C. C—, 5-26	Series D. C—, 5-26	No. Strains
1	0.00002 cc.	+ 24 hours.	+ 18 hours.	+ 18 hours.	+ 18 hours.	+ 24 hours.
2	0.002 cc.	+ 18 hours.	+ 24 hours.	+ 18 hours.	+ 24 hours.	.....
3	0.0002 cc.	+ 24 hours.	+ 42 hours.	+ 42 hours.	+ 42 hours.	+ 24 hours.
4	0.00002 cc.	+ 12 hours.	+ 12 hours.	+ 12 hours.	+ 12 hours.	.....
5	0.00002 cc.	+ 24 hours.	+ 24 hours.	+ 24 hours.	+ 24 hours.	+ 18 hours.

Cultures positive.

## RESULT JUNE 16, 1913.

No.	Culture Dose	Series E. Normal Serum	Series F. C— Serum, 5-31
1	0.02 cc.	+ 19 hours culture +	+ 18 hours culture +
2	0.002 cc.	+ 42 hours culture +	+ 42 hours culture +
3	0.0002 cc.	+ 42 hours culture +	Lived.
4	0.00002 cc.	+ 66 hours culture +	Lived.
5	0.000002 cc.	+ 42 hours culture +	+ 66 hours culture 0.

There was definite, though not strong, protective power, but only in the one specimen, taken after the temperature permanently had reached normal. Some of the negative results obtained in previous cases are probably due to failure to test the serum at repeated intervals, as has been pointed out by Dochez.

## PHAGOCYTOSIS TESTS.

No.	Leucocytes.	Culture Strain Suspended In.	Serum.	Result.
1	Normal blood.	C— normal serum.	Normal.	Almost 0.
2	Normal blood.	C— serum, 5-21.	C—, 5-21.	Almost 0.
3	Normal blood.	C— serum, 5-23.	C—, 5-23.	Almost 0.
4	C— blood, 5-23.	C— serum, 5-23.	C—, 5-23.	Almost 0.
5	Normal blood.	C— in salt solution.	Normal.	0
6	Normal blood.	C— in salt solution.	C—, 5-26.	0
7	C— blood, 5-26.	C— in salt solution.	C—, 5-26.	0
8	C— blood, 5-26.	P— in C— serum, 5-26.	C—, 5-26.	0
9	C— blood, 5-26.	D— in C— serum, 5-26.	C—, 5-26.	0
10	C— blood, 5-26.	S— in C— serum, 5-26.	C—, 5-26.	0
11	Washed leucocytes.	C— in salt solution.	Normal.	0
12	Washed leucocytes.	C— in salt solution.	C—, 5-26.	++
13	Washed leucocytes.	C— in salt solution.	C— heated at 56°C.	++
14	Washed leucocytes.	C— in salt solution.	C—, 5-26 (diluted 1-3).	++
15	Washed leucocytes.	C— in salt solution.	(Diluted 1-10).	0
16	Washed leucocytes.	C— in salt solution.	C—, 5-31.	++ to ++
17	Washed leucocytes.	P— bl. in salt solution.	C—, 5-26.	0
18	Washed leucocytes.	W— bl. in salt solution.	C—, 5-26.	0

This table shows that the culture C— was not phagocytized at all in normal serum, nor in the serum of the patient early in the disease. With the fall in temperature, the serum acquired the power of promoting phagocytosis of this one corresponding strain, but not of five other heterologous strains, all of which had been shown to be susceptible to the action of their own homologous serum. This power appeared at a

time when efficient protective power had not yet appeared. It was more marked than usual, in being evident in a 1 to 9 dilution of serum, but not in a 1 to 30 dilution.

CASE XV.—R. P., colored male, 24 years old, was admitted May 28, 1913, on the third day of the disease, with consolidation of the right upper and middle, and left upper lobes. The pneumococcus was cultivated from the blood on the third day, and again on the fourth day, when 175 colonies per cubic centimeter appeared on the plates. A sputum strain was also obtained by plating on the third day. Death occurred on the sixth day. The serum was obtained on the third day. This man lived in the same house as did Case XVI, and was taken sick two days later than he.

CASE XVI.—D. W., colored male, 27 years old, was admitted May 28, on the fifth day, with consolidation of the right lower lobe. Blood culture on admission was negative. The culture used was plated from the sputum on the fifth day. The temperature fell by crisis on the eighth day. Serum was obtained on the fifth day (May 28), eighth day (crisis, May 31), and ten days after crisis (June 10).

## PRELIMINARY VIRULENCE TESTS (MICE).

No.	Dose.	Series A. P— Blood.	Series B. P— Sputum	Series C. W—
1	0.000002 cc.	+ 48 hours.	+ 48 hours.	.....
2	0.00002 cc.	+ 48 hours.	+ 48 hours.	+ 48 hours.
3	0.0002 cc.	+ 48 hours.	+ 48 hours.	.....
4	0.002 cc.	+ 24 hours.	+ 24 hours.	.....
5	0.02 cc.	+ 24 hours.	+ 24 hours.	.....

All three strains were of high virulence for mice; and the blood and sputum strains of P— were of equal virulence.

## PHAGOCYTOSIS TESTS.

No.	Leucocytes.	Culture Strain Suspended In.	Serum.	Result. Deg. of Phagocytosis.
1	Washed, normal	P— sputum in salt sol.	+ Normal human.	—
2	Washed, normal	P— sputum in salt sol.	+ P— serum.	—
3	Washed, normal	P— blood in salt sol.	+ Normal human.	—
4	Washed, normal	W— in salt solution +	Normal human.	++
5	Washed, normal	W— in salt solution +	W—, 5-28.	++
6	Washed, normal	P— sputum in salt sol.	+ Normal human.	0
7	Washed, normal	P— blood in salt sol.	+ Normal human.	0
8	Washed, normal	W— in salt solution +	Normal human.	0
9	Washed, normal	P— sputum in salt sol.	+ Norm. rabbit, fresh.	0
10	Washed, normal	P— sputum in salt sol.	+ Norm. mouse, fresh.	0
11	Washed, normal	P— blood in salt sol.	+ Norm. rabbit, fresh.	0
12	Washed, normal	P— blood in salt sol.	+ Norm. mouse, fresh.	0
13	Washed, normal	W— in salt solution +	Norm. mouse, fresh.	0
14	Washed, normal	W— in salt solution +	Norm. rabbit, fresh.	0
15	Washed, normal	P— blood in salt sol.	+ P— serum, 56°C.	0
16	Washed, normal	P— blood in salt sol.	+ W—, 5-31, 56°C.	++
17	Washed, normal	W— in salt solution +	P— serum, 56°C.	0
18	Washed, normal	W— in salt solution +	W— ser., 5-28, 56°C.	++
19	Washed, normal	W— in salt solution +	W— ser., 5-31, 56°C.	++
20	Washed, normal	W— in salt solution +	W— ser., 6-10, 56°C.	++
21	Washed, normal	W— in salt solution +	W— ser., 5-31, 56°C. (diluted 1 in 3).	++
22	Washed, normal	C— in salt solution +	W— ser., 5-31, 56°C.	0
23	Washed, normal	P— in salt solution +	W— ser., 5-31, 56°C.	0
24	Washed, normal	Neufeld Pn in salt sol.	+ W— ser., 5-31, 56°C.	0
25	Washed, normal	R— in salt solution +	W— ser., 5-31, 56°C.	0
26	Washed, normal	S— in salt solution +	W— ser., 5-31, 56°C.	0
27	Washed, normal	D— in salt solution +	W— ser., 5-31, 56°C.	0

A study of the tests which were repeated several times with identical results, and which are summarized in the table above, reveals some very interesting facts. All three strains, which had shown a high virulence for mice, were readily phagocytizable in fresh normal human serum. These were the only strains met with, isolated during the acute stage of the disease, which were phagocytizable at all (when isolated) in fresh

normal serum, and, at first sight, it would seem probable that they were to be regarded as exceptional cases, where a low virulence for man did not run parallel with the high virulence for laboratory animals. This view is supported by the fact that none of the three strains were phagocytizable in fresh normal rabbit, or mouse serum. As regards the sputum strains the objection might be raised (improbable though it be, since the cultures on the plates were practically pure) that the colonies subcultured were accidental contaminations from the mouth, and did not represent the infecting strain. Such an objection cannot be raised to the blood culture isolation, which behaved identically like the other two. It seems highly improbable, too, that a strain is to be regarded as avirulent for man, when it is isolated from the blood of a patient critically ill two or three days before death. This would seem to be the best available criterium of virulence for man. There was no possibility of a change taking place in the culture after isolation, since these results were obtained in tests on May 30, after but one generation on artificial media. While a single exception is not sufficient to overthrow a rule, it suggests the advisability of using greater caution in regarding the virulence of a strain for man as always running inversely parallel with its phagocytizability in human serum.

While there was no conspicuous difference between the phagocytic activity of this patient's serum and that of normal serum when fresh, striking differences in their behavior appeared after inactivation. All three strains were quite resistant to phagocytosis in inactive normal serum (heated at 56° C., or after standing one week on ice), and were likewise not affected by the heated serum of either patient at the height of the disease. But the heated serum of the patient who recovered (W—), obtained at the crisis and (to a slightly less degree) also that obtained ten days after crisis, caused active phagocytosis of the homologous strain and also of the strains of P—, who probably had been infected directly by W—. It did not influence any of the other heterologous strains tested, in particular not that from C—, whose serum had caused phagocytosis of his own strain, but not of the strains from P— or W—.

In order to test the parallelism of the phagocytic activity and the protective power of the sera, the following series of mice were inoculated, using mixtures of serum and diluted culture.

No.	Dose of Culture C—	Series A. Normal Serum.	Series B. W— Serum, 5-31.	Series C. W— Serum, 6-10.
1	0.002 cc.	—	—	—
2	0.002 cc.	—	—	—
3	0.0002 cc.	—	—	—
4	0.00002 cc.	—	—	—

There was efficient protection by W—'s serum obtained at crisis, for the strain P— blood, but none by P—'s serum, obtained during the acute stage of the disease, three days before death. The protective power here ran parallel with phagocytic activity.

No.	Dose of Culture C—	Series A. Normal Serum.	Series B. W— Serum, 5-31.
1	0.002 cc.	—	+ 24 hours.
2	0.002 cc.	—	+ 40 hours.
3	0.0002 cc.	—	+ 24 hours.
4	0.00002 cc.	—	+ 66 hours.

Here again the lack of protective power of W—'s serum for the heterologous strain C—, parallels its inactivity in vitro.

No.	Dose of Culture W—	Series A. Normal Serum.	Series B. W— Serum, 5-28.	Series C. W— Serum, 5-31.	Series D. W— Ser., 6-10.
1	0.02 cc.	+ 40 hrs. cult. +	+ 40 hrs. cult. +	Lived.	Lived.
2	0.002 cc.	+ 48 hrs.	+ 66 hrs. cult. +	Lived.	Lived.
3	0.0002 cc.	+ 40 hrs. cult. +	+ 40 hrs. cult. +	+ 6 days cult. +	+ 6 days cult. +
4	0.00002 cc.	+ 4 days cult. +	+ 4 days cult. +	+ 6 days cult. 0. Lived. (Pericardial hemorrhage).	+ 6 days cult. 0.
5	0.00002 cc.	+ 5 days cult. +	+ 40 hrs. cult. +	Lived.	+ 6 days cult. 0.

There was very efficient protective power in the serum of W— obtained at, and again ten days after the crisis, toward the homologous strain, whereas the serum three days before the crisis was no more active than was normal serum. This is parallel with the phagocytic activity of the heated serum.

To determine the parallelism of the phagocytic action of the sera in vivo and in vitro, studies were made of the sera of R— and of W—, which had shown the most marked protective power. Each of a series of mice were injected intraperitoneally with 0.2 cc. of the serum of R— obtained after lysis, and each of a control series with the same quantity of normal serum. Three hours later 0.02 cc. of culture R— was injected intraperitoneally in each mouse. Specimens of the exudate were removed at intervals with a capillary pipette, and stained with methylene blue. In the control animals receiving normal serum there was unrestricted multiplication of the organisms, which remained exclusively extra-cellular, and after one and two hours were present in the exudate in enormous numbers. In the protected animals there was no such multiplication evident. (The total number of organisms introduced in this dose is relatively small, and one must search very carefully to find any organisms.) After one-half, and one hour nearly all (though not quite all) the extra-cellular cocci had disappeared from the exudate and scattered leucocytes were seen containing one or more pair of ingested cocci. These were more numerous (as shown by Ungermann<sup>25</sup>) in smears made directly from the peritoneal surfaces. There was no evidence of extra-cellular lysis.

More definite pictures were obtained by the use of W— serum<sup>26</sup> and culture. All the mice were prepared by injecting 1 cc. of sterile broth intraperitoneally 24 hours before the test. Mixtures were prepared, each containing 0.2 cc. of patient's serum and 0.2 cc. of a broth culture of the pneumococcus W—, and were injected into the peritoneal cavity of a series of mice, a second series receiving the same quantities of broth culture and normal serum. Specimens were removed with a capillary pipette at fifteen minute intervals.

After fifteen minutes in the normal serum controls the exudate contained many diplococci, all extra-cellular, and there was no evidence of phagocytosis. After one hour these had increased greatly in number. In the protected (postcritical serum) animals, even after fifteen minutes, the great majority of the extra-cellular organisms had disappeared, though a few scattered ones could be found until after the lapse of an hour. After fifteen minutes a considerable number of cocci were found inside the leucocytes, though the number found did not seem to account for all that had disappeared. After one-half hour there were about the same number of ingested cocci to be seen. After one hour but few were left, even in smears made directly from the peritoneal surfaces. This disappearance, in large part at least, is due to intracellular digestion. Even after fifteen minutes some of the ingested cocci stain poorly, and show evidences of solution. The same process is seen when the serum mixtures are injected into untreated mice, except that it takes place more slowly. There was no evidence of extra-cellular lysis.

In all of the four sera examined the activity was retained after heating one-half hour at 56° C. In some cases it was somewhat reduced. If the heating was prolonged, or if it much exceeded 56° C., the activity was destroyed. It persisted for several weeks in serum stored on ice, but gradually weakened, and finally disappeared. Except in one case dilution with salt solution destroyed its activity. The activity could never be increased or restored by adding fresh normal serum. The substances are, therefore, tropines, rather than immune opsonines. They are removed from the serum by digestion with the organism on which they act.

The strict limitation of the activity of each serum to the homologous strain is surprising, in view of the findings of Neufeld and of Cole, that most strains can be classified in a small number of groups. The explanation probably is that each strain differs to a certain extent from all, or most, other strains in its serum reactions. 'A serum as feeble as are the patient's sera, can show activity only under most favorable conditions; *i. e.*, when tested with the homologous strain of pneumococcus. But a more potent immune serum, even though univalent, might act about equally on all those strains most closely related to the one used in producing the immune serum. The slight differences between the strains would thus be obscured and they would all fall apparently into a single group. Neufeld's work' indicates that this grouping of strains of pneumococci is not absolute, but that a very potent univalent serum while largely limited in its action to members of the corresponding group, may exert a certain amount of "overlapping" activity on members of other groups. It is interesting that none of the last three active sera tested showed any action on Neufeld's strain PnI, kindly furnished by Dr. Dochez as a typical example of the commonest group.

Of the sixteen cases, one has been omitted from the summary because it was tested only with an heterologous stock culture. A second one was also omitted because the strain isolated was so feebly virulent for mice that no definite con-

clusions as to the protective power of the corresponding serum could be drawn.

The results of these experiments may be summarized as follows:

Of twelve cases, in which satisfactory protection tests were carried out with the sera of patients after crisis, or lysis, using the homologous strain of pneumococcus, nine had sera which showed definite protective power for mice as compared with normal serum. The sera of three gave negative results; in these three cases but one specimen of serum was tested.

In two of the cases, the serum of which showed protective power after the crisis, specimens of serum obtained during the acute stage of the disease showed no such power. Further in two other cases, one fatal, in which the serum was examined only during the acute stage, no protection was manifested.

Three sera, which protected mice from the homologous strain, were also tested with an heterologous strain, and showed no protective power toward that strain.

Occasionally protective power cannot be demonstrated unless the serum is tested at frequent intervals during convalescence.

With but two exceptions, all the strains isolated were not phagocytal in fresh normal human serum, and were presumably virulent for man. The other two strains, which seemed identical with one another in every respect, were highly virulent for mice. As one was cultivated from the blood of a patient a few days before death, it seems most reasonable to regard it as also virulent for man, in spite of its phagocytability in normal human serum. This suggests the advisability of greater caution in assuming that the virulence of an organism for man is always parallel with its resistance to phagocytosis in the test tube.

Of eleven cases in which the phagocytic activity of the serum after crisis, or lysis, was tested in vitro, six showed definite activity. In five, negative results were obtained. In some of these, at least, positive results would probably have been obtained had suitable variations in technic been employed.

This activity has a significance which is quite different from that of a rise in opsonic index, which has often been described, but is qualitatively comparable with the activity of potent immune serum, in that it brings about *active phagocytosis of a virulent pneumococcus, not phagocytal in normal human serum.*

In two of these cases serum examined before the crisis showed no such activity. The serum of a fatal case was also inactive.

This phagocytic activity, with one exception was *strictly limited to the homologous strain*, derived from the patient whose serum was being tested.

The active substances in the serum are bacteriotropines, in the sense of Neufeld, since they resist heating at 56° C., and persist in the serum in vitro, for a considerable period.

In both of two cases tested, phagocytosis in the peritoneum of the mouse closely paralleled phagocytosis in the test tube. Intracellular digestion of the cocci, as shown by changes in staining reaction, was marked in both cases.



The phagocytic activity of the serum ran closely parallel with its protective power for mice, both in incidence, in time of appearance, and in strict specificity as to the strain of pneumococcus affected. It, therefore, seems justifiable to conclude that the protective action of the serum depends on, and is due directly to, its power of promoting phagocytosis.

A much larger number of cases must be studied and the constancy of the process demonstrated before drawing final conclusions as to the rôle it plays in man. But the fact that such definite phagocytic activity can be shown to develop at the crisis (or lysis) in at least a considerable proportion of cases, and that this activity is directed against, and largely limited to, the one virulent strain infecting the patient, makes it seem probable that this factor plays an important part in bringing about recovery in man.

In conclusion, I wish to express my thanks to Dr. Lewellys F. Barker for permission to study and report these cases, and also Dr. R. H. Major, Dr. T. P. Sprunt, and especially Dr. J. A. Luetscher for suggestions and assistance in carrying out the work.

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## LECTURES ON THE HERTER FOUNDATION.

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LECTURE III.<sup>1</sup>

(With 22 text-figures.)

## PIROPLASMOSIS.

The diseases included under the general term of piroplasmosis are amongst the most devastating which affect domesticated animals, and they are, consequently, of great economic importance. As far as known, all forms of piroplasmosis are tick-transmitted.

## DISEASES DUE TO PIROPLASMA (= BABESIA).

Strictly interpreted, the term "piroplasmosis" applies to diseases caused by intracorporeal parasites belonging to the genus *Piroplasma* (= *Babesia*), which possess certain definite characters, produce definite symptoms, and are communicable by blood inoculation.

The striking features which characterize *Piroplasma* are the following: On examining the infected blood corpuscles and enumerating them in accordance with the types of parasites they contain it will be found that 30 to 40 per cent contain two *piriform* parasites joined at their tapering extremities—this appearance is characteristic of what I regard as the genus *Piroplasma*, of which the species *canis*, *caballi*, *ovis*, *bovis* or *bigeminum*, and *divergens* may be taken as examples. Of the remaining infected corpuscles about 50-70 per cent contain single parasites of varying form, whilst a few (anywhere from 0.5 to 11 per cent) show characteristic dividing forms, whose significance I pointed out some years ago with Graham-Smith. *Piroplasma canis* and *P. pitheci* differ slightly from other piroplasms in that some infected corpuscles (about 1-4 per cent) contain more than two parasites (i. e., 4-16), although in *P. bovis* four parasites are occasionally found within a corpuscle. The usual mode of multiplication of *Piroplasma* is shown in the accompanying figure (Fig. 1).

True piroplasmosis occurs in cattle, sheep, horses and dogs in many parts of the world. The parasites which cause the disease in each of these species of mammals are specific in respect to their pathogenic action: for instance, the parasite

<sup>1</sup> Owing to this lecture not having been written until after it was delivered in the Medical Department of the Johns Hopkins University, October 10, 1912, the author has taken the opportunity of adding a considerable amount of new matter and has somewhat altered the form of the lecture.

Figures I, IV, VI, XI, XII, XX-XXII are reprinted from *Parasitology*, Vols. I-V; figures III and V are reprinted from *Ticks*, Part 2; the remaining twelve figures (II, VII-X, XIII-XIX) have not hitherto been published. All except figure XI are by the author.

<sup>2</sup> The generic name *Babesia* has priority, and is coming into general use, although the name *Piroplasma* is more usually employed by American and British writers.

which occurs in the dog (*P. canis*) is only capable of setting up the disease in the dog. Parasites having the morphological characters of *Piroplasma* have been discovered in the monkey and rat (*P. pitheci*, *P. muris*), but the symptoms they produce and their mode of transmission are unknown.

In the domesticated animals above enumerated, the presence of piroplasms in the blood is accompanied by a definite train of symptoms following upon the animals being attacked by pathogenic ticks. Usually about 8-10 days after the animals have been attacked by the ticks they show high fever, loss of appetite, hæmoglobinuria, icterus, and a large number of the animals die in a few days, anywhere from 25-100 per cent succumbing to the infection. The hæmoglobinuria is chiefly due to the destruction of the blood corpuscles by the parasites, the hæmoglobin being eliminated from the kidneys. The urine may appear lightly tinged with hæmoglobin or very dark, depending upon the intensity of the blood destruction. In severe cases the number of corpuscles in the circulating blood may be reduced to a third or less, the blood, consequently, appearing thin and watery. When animals "recover" they do so slowly, and the parasites grow very scarce in the blood, so that they cannot, as a rule, be detected microscopically.

The parasites persist in the blood of "recovered" animals for years after they have, to all outward appearances, resumed a healthy condition. "Recovered" or "salted" animals are not susceptible to reinfection, and consequently possess enhanced value in countries where piroplasmosis is endemic. The blood of "salted" dogs and cattle has been found to be infective for three to eight years after the acute attack has subsided. In nature, piroplasmosis is only transmitted by ticks which have previously fed upon infected animals, either in the acute stage of the disease or in the "salted" condition. It is owing to indigenous animals being "salted" in regions where piroplasmosis is endemic that the ticks of the region continue to harbor the parasite and constitute a potential source of danger to freshly imported animals coming from places where the disease is absent.

## BOVINE PIROPLASMOSIS.

Bovine piroplasmosis is due to at least two species of *Piroplasma*: *P. bovis* and *P. divergens*.

The latter parasite (Fig. II), judging from specimens which have reached me hitherto, is confined to Europe and in nature is transmitted by *Ixodes ricinus* (Fig. III), the common European cattle tick. I have received specimens of *P. divergens* and *I. ricinus* from cattle suffering from "redwater" in Norway, Germany, Russia, Hungary, Great Britain, and Ireland, and I know that this form of redwater occurs in Finland, Sweden and France, where *I. ricinus* is prevalent. The transmission of the disease by means of larval stages of





*I. ricinus*, the progeny of ticks collected from diseased cattle suffering from piroplasmosis in Germany, England and Ireland, has been demonstrated experimentally by Kossel and his colleagues, by Stockman, and by me, respectively. Although the symptoms due to *P. divergens* infection are similar to those produced by *P. bovis*, the disease appears to be milder. Animals which have "recovered" from *P. divergens* infection are susceptible to infection with *P. bovis*. The parasites, moreover, show distinct morphological differences which were recognized by Kossel and others, although it is but recently that MacFadyean and Stockman gave *P. divergens* its distinctive name.

The well-known Texas fever of the United States, generally known as redwater or bovine hæmoglobinuria in other parts of the world, is due to *P. bovis* (Fig. IV) and appears to be transmitted in nature almost solely by *Boophilus annulatus* and its varieties, *B. australis* and *B. decoloratus* (Fig. V).

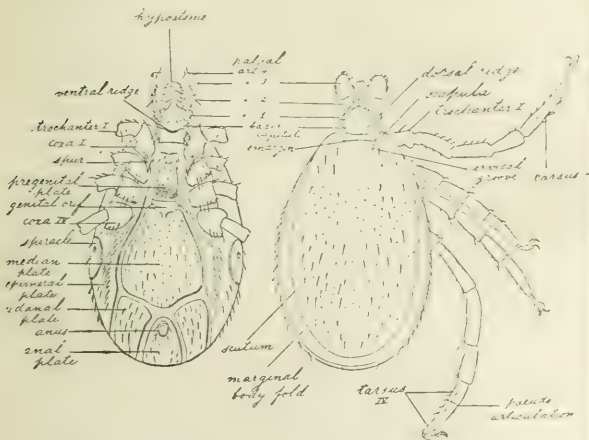


FIG. III.—*Ixodes ricinus* ♂, venter and dorsum. (Nuttall, 1908.)

*Piropasma bovis* is widely distributed in warm countries and the tropics; it occurs in North and South America, Australia, Asia and Africa, and occasionally in Southern Europe. Redwater has been repeatedly reproduced experimentally by means of larval *Boophilus*, the progeny of ticks which have sucked the blood of animals suffering from redwater. This form of piroplasmosis has been the cause of great financial losses, it having been estimated that in the United States alone the annual loss has amounted to forty million dollars.

#### EQUINE PIROPLASMOSIS.

Redwater, or "biliary fever," in horses, as I have shown with Strickland, is due to two parasites which are morphologically distinct: *Nuttallia equi* (Laveran), of which I shall speak presently, and *Piropasma caballi* Nuttall (Fig. VI), the cause of true piroplasmosis in equines. When a horse "recovers" from *P. caballi* infection it is still susceptible to *N. equi* infection. *Piropasma caballi* occurs in Russia, Rou-

mania, in Transcaucasia, and apparently extends across Siberia. *Dermacentor reticulatus* has been shown by experiment to transmit the disease, and this tick is distributed over the geographical area mentioned, besides occurring in Western Europe, including Great Britain, where it is, however, relatively rare. Although I have received blood-films from horses suffering from biliary fever in other parts of the world, none of the films contained parasites similar to *P. caballi*.<sup>2</sup>

#### OVINE PIROPLASMOSIS.

True piroplasmosis, due to *P. ovis*, has been observed in sheep in Italy, Turkey, Roumania and Transcaucasia. I have been informed that it has recently been discovered in Egypt.<sup>4</sup> The recorded presence of ovine piroplasmosis in South Africa and North America is due to errors of observation. It has been demonstrated by experiment that *Rhipicephalus bursa* conveys the disease. The geographical distribution of this tick, judging from specimens which have reached me, appears to be limited chiefly to Southern Europe, the Islands in the Mediterranean, Transcaucasia, and North Africa, although

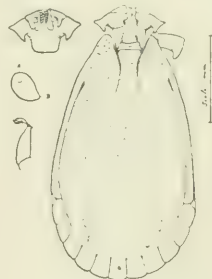


FIG. VII.—*Haemaphysalis leachi* ♂. (Original, G. H. F. N. del.)

Neumann states that it occurs both in East and West Africa as far as the Cape and also in the West Indies. I have only seen *P. ovis* in blood-films from Roumania and Italy.

#### CANINE PIROPLASMOSIS.

Two forms of piroplasmosis have been observed in dogs, the commoner and more widely distributed being due to *P. canis*. In India *P. canis* (Fig. I) is transmitted by *Rhipicephalus sanguineus*, a tick which has accompanied the dog practically all over the world. This tick is the probable vector of *P. canis* throughout Asia, Southern Europe and North Africa. *Haemaphysalis leachi* (Figs. VII-X), on the other

<sup>2</sup> On 17 January, 1913, Dr. S. T. Darling, Chief of the Department of Sanitation, Ancon, Panama, sent me a blood-film showing *P. caballi*, taken from a horse in Panama. The ticks he sent us for determination, and which were taken from the horse, were *Dermacentor nitens* and *Amblyomma cajennense*—it is probable that the former is the carrier, since it is usually found on horses.

<sup>4</sup> In blood-films received, 5 VI, 1913, from Mr. F. E. Mason, M. R. C. V. S. of Cairo, we were only able to detect a few small single intracorporeal parasites, none of which were typical of true piroplasms.

hand, is the vector over the greater part of Africa from Cape Colony northwards. Attempts to infect the fox and jackal with the parasite have been attended by failure.

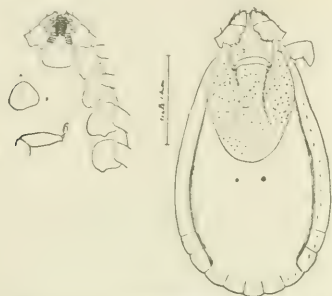


FIG. VIII.—*Haemaphysalis leachi* ♀.  
(Original, G. H. F. N. del.)

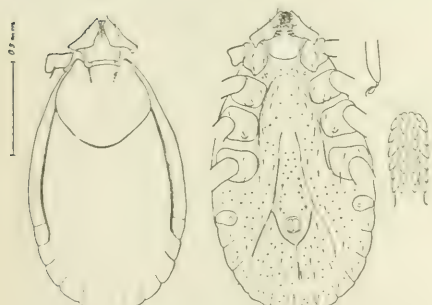


FIG. IX.—*Haemaphysalis leachi* nymph. (Original,  
G. H. F. N. del.)



FIG. X.—*Haemaphysalis leachi* larva.  
(Original, G. H. F. N. del.)

On the other hand, another parasite (*P. gibsoni* Patton), which is somewhat different to *P. canis* morphologically, is stated to produce infection both in dogs and jackals in India.

#### CONCERNING THE TICKS WHICH TRANSMIT PIROPLASMA.

As I have already stated, piroplasmosis is conveyed to cattle by *Boophilus* and *Ixodes ricinus*, to sheep by *Rhipicephalus bursa*, to dogs by *Rhipicephalus sanguineus* and *Haemaphysalis leachi*, and to horses by *Dermacentor reticulatus*. A number of other species of ticks may, no doubt, play a part as carriers, but the ones I have named are the chief vectors, and in each case they have been proved to transmit piroplasmosis under experimental conditions.

Since piroplasmosis only occurs in the presence of ticks, it is now generally recognized that to grapple with the problem of prevention a knowledge of their life habits is essential. At the time at my disposal I can only refer briefly to the subject. All Ixodid ticks lay eggs, whence they emerge as hexapod larvæ. As soon as their chitinous exoskeleton has hardened sufficiently, the larvæ may feed upon a vertebrate host. After feeding they remain quiescent for a period, after which they moult and emerge as nymphs. These feed again, undergo metamorphosis, and finally emerge as adult males or females. In the case of *Boophilus* we have a one-host tick, for it remains, as a rule, upon the host from the larval to the adult stage, moulting twice whilst remaining upon the host. In *R. bursa* we have a two-host tick, since it remains upon the host during its larval and nymphal stages, moulting once upon the host; it abandons the host as a fully-fed nymph, undergoes its metamorphosis upon the ground, and emerges as an adult, which has to seek a second host. All of the remaining pathogenic species of ticks above enumerated are three-host ticks, for they drop from the host when replete, both in the larval and nymphal stages, to undergo their metamorphosis upon the ground; in other words, the larva, nymph and adult have each to seek a host. In all of the ticks here mentioned the sexes copulate upon the host, and the replete fertilized females drop to the ground, where they seek shelter and oviposit. The number of eggs laid varies with the species and individual. Taking average figures from my raising notes:

<i>Boophilus decoloratus</i> lays.....	1200-4500 eggs
<i>Ixodes ricinus</i> lays .....	2400-3200 eggs
<i>Rhipicephalus bursa</i> lays .....	4900-6900 eggs
<i>Rhipicephalus sanguineus</i> lays.....	ca 2000-3000 eggs
<i>Haemaphysalis leachi</i> lays .....	2400-4800 eggs

The rate of metamorphosis varies considerably according to the temperature at which the ticks are maintained. In *Boophilus*, the life-cycle is rapidly completed, because the tick is incubated upon the warm-blooded host throughout its parasitic period, and it does not lose time in having to find a host after each ecdysis. In *Boophilus*, the cycle from egg to egg may last 120 days; in *R. bursa* it lasts somewhat longer; in *I. ricinus* it lasts 178 days, these being minimum periods observed under experimental conditions.

#### BEHAVIOR OF PIROPLASMA IN TICKS.

When a fertilized female tick has fed upon an infected animal the parasites she imbibes undergo development within her body. About the fourth or fifth day after the parasites have entered the tick's gut there appear free, club-shaped

bodies, which move about with vermiform movements and are encountered in the gonads. Their further development is obscure, but in infective ticks both Christophers (Fig. XI) and Marzinowsky have found minute bodies, which may provisionally be called Sporozoites, in the salivary glands.

In *Boophilus* and *Ixodes* the larvæ, descended from infected parents, are infective. In *H. leachi* the larvæ and nymphs are not infective; the ticks, descended from an infected parent, only infect the host when they have attained maturity (Lounsbury, Nuttall). In *R. sanguineus* the larvæ are not infective, but the nymphs and adults are; when nymphs are fed on an infected host the adult tick is infective (Christophers). With *R. bursa* (two-host tick) the larvæ are not infective, but the adults are (Motas). I have found adults of *H. leachi* infective after starving for seven months, and believe that ticks harboring *Piroplasma* remain infective as long as they live.

Unfed ticks may withstand prolonged starvation. I have seen unfed larvæ of *I. ricinus* still lively after 176 days starvation; *B. annulatus* larvæ were lively after 251 days starvation;

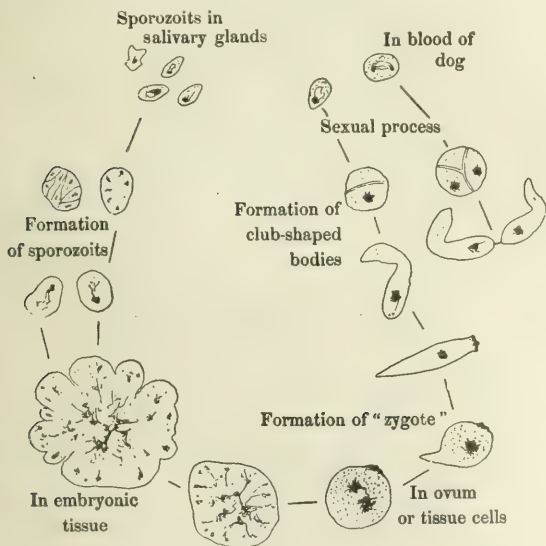


FIG. XI.—*Piroplasma canis*, showing the developmental cycle in *Rhipicephalus sanguineus* according to Christophers, 1912.

*R. bursa* adults were lively after 343 days starvation. In this connection I only mention the longevity of stages which may transmit piroplasmosis. It is clear that three-host ticks are the most difficult to eradicate by treating infested animals with tick-destroying dips or by removing the hosts from infested pastures for prolonged periods of time with the object of starving the ticks.

#### DISEASES DUE TO NUTTALLIA.

The first parasite belonging to this genus to be discovered was the one occurring in the horse to which Laveran (1901) gave the name of *Piroplasma equi*. As the morphology of

this parasite does not agree with that of a true *Piroplasma*, as defined by me, França (1909) placed it in another genus which he named *Nuttallia*. That he was justified in taking this step is clear from subsequent observations carried out upon the parasite by myself and Strickland in 1910-1912 (Fig. XII), in the course of which we clearly differentiated it from *P. caballi*. Through the courtesy of Professor E. J. Marzinowsky, of Moscow, Russia, I have been able to examine blood-films showing so-called piroplasms in deer and reindeer, and I can also refer these to the genus *Nuttallia*.

*Nuttallia equi* appears to be much more widely distributed than *Piroplasma caballi* (q. v.); it produces a similar disease with hæmoglobinuria and jaundice, etc., in Italy, Sardinia, in

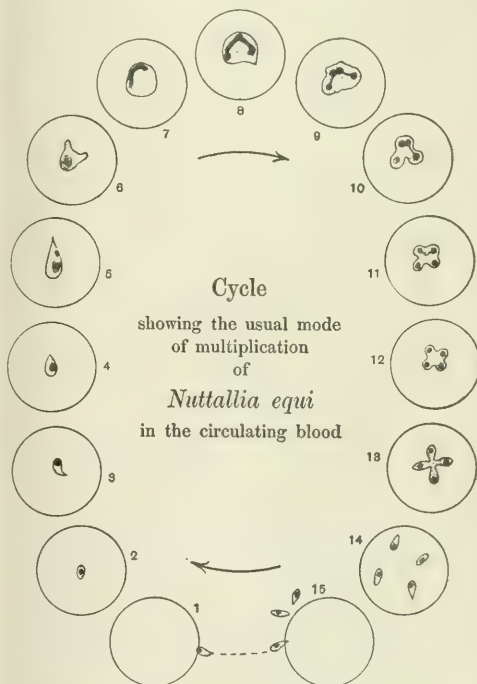


FIG. XII.—*Nuttallia equi*: (1) Entrance of minute oat-shaped parasite into a corpuscle; (2-5) the parasite grows in size whilst continually but slowly altering its shape; (6) larger parasite which is actively amoeboid; (7-10) successive stages of division of the chromatin; (11-15) process of division repeatedly observed in living parasites: the formation and breaking-up of the cross-forms, the scattering of the daughter-cells within the corpuscle, and their escape from the corpuscle. (Nuttall and Strickland, 1912.)

many parts of Africa, Transcaucasia, India, Southern Annam and Brazil, from all of which countries blood-films have been sent to me for examination by correspondents.

Our experiments showed that a horse, after recovery from *P. caballi* infection, succumbed to the inoculation of *N. equi* blood. Conjoined pairs of piriform parasites are never observable in *N. equi* infection; about 90 per cent of the in-



fectured corpuscles contain single parasites of all shapes and sizes, many of them being much smaller than any true piroplasm, 2-5 per cent of the corpuscles contain 2 to 4 parasites, and 1-5 per cent contain dividing, or "cross-forms." The accompanying diagram represents our conclusions as to the usual mode of multiplication of *N. equi* in the circulating blood. We studied the parasite in the living condition as well as in stained films.

Nuttalliosis resembles piroplasmosis in its symptomatology and pathology. I have a "salted" horse whose blood was virulent when last tested, a period of three years having elapsed since it was first infected. In Africa, as first shown by Theiler, the parasite is transmitted by *Rhipicephalus evertsi*. This tick, when fed upon infected horses in its larval and nymphal stages, is infective when adult. We do not know what species of tick serves to carry the parasites in other parts of the globe.

#### EAST COAST FEVER OF CATTLE.

This devastating disease, which appears to be confined to Africa, is ushered in by the onset of fever following upon an

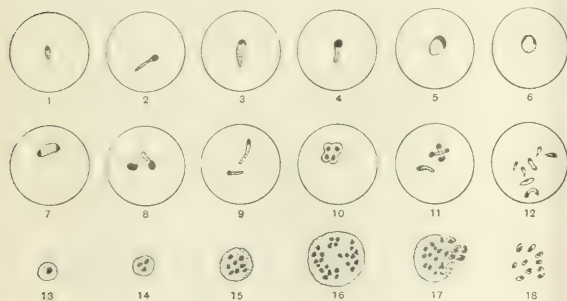


FIG. XIII.—*Theileria parva*: (1-12) stained intracorporal parasites; the figures arranged arbitrarily in a manner which would appear to indicate that they may divide into two or four parasites at a time, although division has not been observed to take place in living parasites; (13-18) Koch's bodies, a series of stained parasites from a spleen smear, likewise arranged arbitrarily in sequence to indicate their probable mode of development from uninellular bodies; (17 and 18) represent the breaking-up of the Koch's body and the liberation of its component elements. The black denotes chromatin, the stippling denotes the blue-staining protoplasm (Giemsa stain). (Original, and from Nuttall and Fantham, 1910.)

incubation period of 10-20 days after the cattle have been attacked by the ticks which convey the parasite. The fever continues usually for about 12 days, death taking place 18-34 days after the ticks have attacked the host. The characteristic symptoms of redwater, hemoglobinuria, icterus and anaemia are absent in East Coast Fever. The mortality may amount to 80-90 per cent. Cattle which are immune to redwater are susceptible to East Coast Fever. In marked contrast to what is observed in redwater we find in East Coast Fever, as the disease progresses, that there is no appreciable decrease in the number of red blood corpuscles present in the peripheral circulation.

The cause of the disease, *Theileria parva* (Fig. XIII),

differs in important respects from the parasites I have previously mentioned, and the disease cannot be communicated by the inoculation of blood containing the parasite, even when large quantities—up to seven litres—are injected.

*Theileria parva* is conveyed by *Rhipicephalus appendiculatus*, *R. simus*, *R. evertsi*, *R. nitens* and *R. capensis*, the first-named species of tick being the usual carrier. The parasites are not hereditarily transmitted in *Rhipicephalus*, but when taken up by the carrier at one stage of its development the tick is infective in the succeeding stage. When *R. appendiculatus* (Figs. XIV-XVII), for instance, sucks *Theileria*-infected blood as a larva the tick is infective as a nymph, or, having sucked infected blood as a nymph, it is infective as an

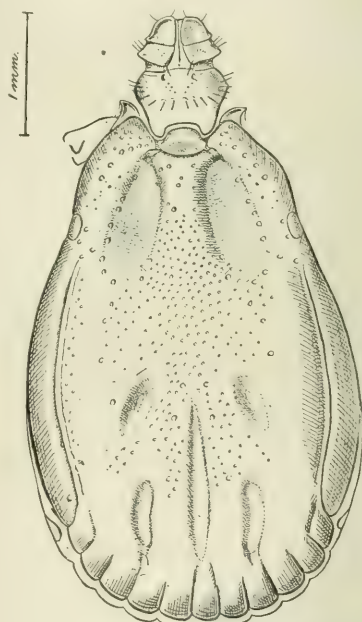


FIG. XIV.—*Rhipicephalus appendiculatus* ♂. (Nuttall, 1913.)

adult. Whereas, in redwater the parasites persist in the blood for years after recovery, and "salted" animals are capable of infecting ticks, the contrary holds for *T. parva*, i. e., when animals recover from East Coast Fever they are incapable of infecting the ticks.

The parasites are at first present in small numbers, but 5-6 per cent of the corpuscles being invaded. The number of parasites, as a rule, steadily increases until death, when 60-75 per cent of the corpuscles in the peripheral blood are found to be infected. We have never observed multiplication of the living parasites in corpuscles, but we have seen them in a few rare instances escape from the corpuscles into the plasma. The parasites move about actively within the corpuscles. Whilst the parasite is very pleomorphic, the commonest forms

seen in stained preparations are ovoid or rounded and comma-shaped or clubbed. A proportion of the parasites is bacilli-form. The appearance of the chromatin in some parasites suggests that multiplication may occur within the infected corpuscles, some of which contain up to eight distinct parasites. If, however, multiplication occurs within the corpuscles it must take place very slowly or we should have observed it in the living parasite. It will be of interest to determine, if *Theileria* multiplies in cultures as do malarial parasites and *Piroplasma canis*.

The results of our investigations forced me to the conclusion that the corpuscles merely serve as vehicles for the parasites, wherein they are housed and maintained until they reach

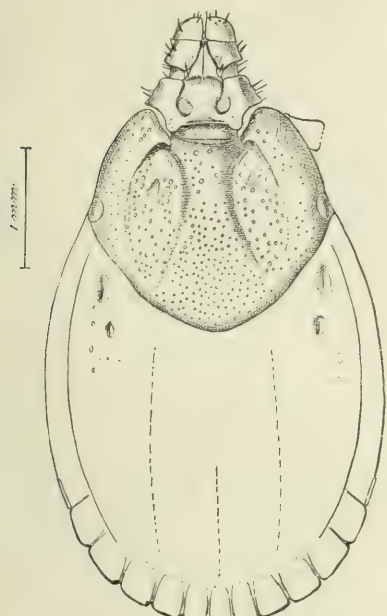


FIG. XV.—*Rhipicephalus appendiculatus* ♀. (Nuttall, 1913.)

their destination within the tick, which serves as their vector. The seat of multiplication and invasion of corpuscles appeared to me to lie in the internal organs, a view which subsequently received support from the investigations of Meyer, who communicated the disease by the intraperitoneal transplantation of large pieces of infected spleen.

Another striking feature connected with these parasites is the occurrence of "Koch's blue bodies" in the internal organs and occasionally in the peripheral blood. These bodies (Fig. XIII, 13-18) were first observed by Koch and to-day are considered to be of prime diagnostic importance. They are termed "blue" because of their appearance in blood-films stained by any of the modifications of the Romanowsky method. When examined stained they usually appear rounded,

the blue-staining protoplasm containing discrete chromatin masses in varying numbers; at times they are seen to be breaking up, each mass of chromatin being accompanied or surrounded by blue-staining protoplasm. These bodies, which were regarded as developmental forms by Koch, have been made the subject of detailed study by Gonder, who states that he has seen them break up into their elements and scatter. They are encountered in the internal organs (lymphatic glands, spleen, etc.) before they appear in the corpuscles of the peripheral circulation. In some cases of East Coast Fever the parasites do not appear in the corpuscles, whilst Koch's bodies only are found in the internal organs. The bodies are found either free in the plasma or in cells—chiefly in lymphocytes—exceptionally in leucocytes. According to Gonder these bodies (which he terms "agamonts") undergo multiplication by schizogony, and I am inclined to agree with him. According to this view the parasites are first uninuclear; they grow, and the nucleus divides repeatedly until many

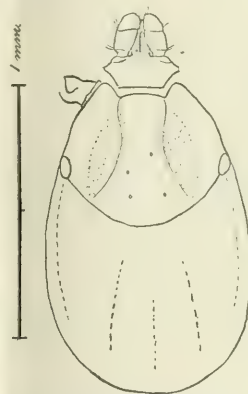


FIG. XVI.—*Rhipicephalus appendiculatus* nymph. (Nuttall, 1913.)

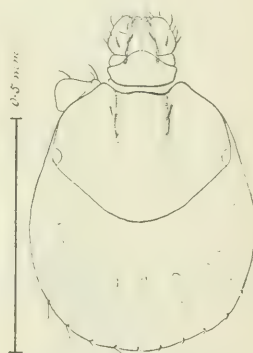


FIG. XVII.—*Rhipicephalus appendiculatus* larva. (Nuttall, 1913.)

small nuclei are formed, after which the minute parasites separate and scatter. It is presumably these small parasites which invade the corpuscles. The rest of the cycle of development, as outlined by Gonder, is so purely conjectural that we can afford to ignore it for the present. It is reasonable to assume, from what I have previously stated, that some of the intracorporal parasites are sexual forms of the parasites destined to undergo further development in ticks. That such a development occurs still remains to be determined, although Gonder believes that he has partially traced it.

#### REMARKS UPON SOME OTHER PARASITES WHICH APPEAR RELATED TO THE FOREGOING.

In the foregoing instances we have dealt mainly with three distinct forms of intracorporal parasites whose mode of transmission, through the agency of ticks, has been demonstrated repeatedly by experiments conducted upon cattle, horses, sheep and dogs. All of these parasites have until



FIG. VI.—*Piroplasma caballi*, showing the same mode of multiplication as *P. canis*. (Nuttall and Strickland, 1912.)

FIG. XIX.—*Nicollia quadrigemina* (Nicolle, 1907): Different stages drawn from a blood-film kindly lent by Professor C. Nicolle. (Original, G. H. F. N. del.)

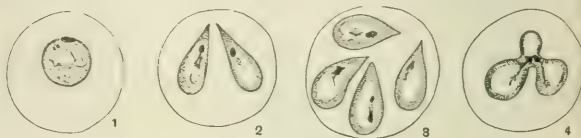


FIG. XVIII.—*Rossiella rossi* (Nuttall, 1910): (1) Single free parasite; (2,3) single uninucleate intracorporeal parasites; (4-12) progressive stages of division into four parasites.



FIG. XX.—Showing the effect of trypanblue treatment upon *Piroplasma canis* in the peripheral blood of a dog: (1-4) normal types of parasites; (5-12) parasites from the same dog, showing progressive degrees of degeneration in blood removed from the dog's ear-vein 6 hours after the injection of the drug. (Nuttall, 1910.)

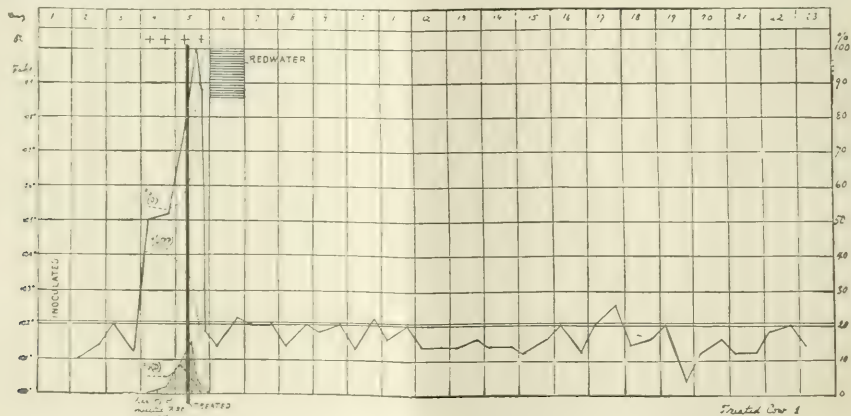


FIG. XXII.—Chart showing the course of events in a trypanblue-treated cow. See description of Fig. XXI. (Treated Cow I. Nuttall and Hadwen, 1909.)



recently been grouped in the one genus, together with certain others to which I shall refer more briefly. It has long been evident to me that the genus *Piroplasma*, or *Babesia*, was being regarded as a "hold-all" for parasites of very varied character, and it appears necessary to separate them more clearly. Dismissing, then, the three genera I have dealt with, viz., *Piroplasma*, *Nuttallia* and *Theileria*, we may consider the following:

"PIROPLASMA MUTANS" THEILER, 1907.

This parasite occurs in cattle in South Africa and Madagascar; it is very minute, resembles *Theileria parva* microscopically but for the absence of Koch's blue bodies, and is likewise transmitted by ticks. Contrary to *Theileria*, the parasite is, however, readily transmitted from animal to animal by blood inoculation, and is practically harmless in respect to pathogenic effects. The parasite is conveyed by *Rhipicephalus simus*, *R. evertsi*, and, rarely, by *R. appendiculatus*. When animals are inoculated a long period of incubation (60-115 days) elapses before the parasites appear in the blood. These data regarding *P. mutans* are based upon the confused accounts given by Theiler and a few statements made by Gonder. I have only studied the parasite in a few stained blood-films. It is clear that the parasite requires to be adequately studied before its position can be determined.

I would refer briefly, moreover, to the following parasites which have been observed in different animals but regarding which we require more information:

*Rossella rossi* (Nuttall, 1910), found in the jackal (*Canis adustus*) in British East Africa. The parasite was referred provisionally by me to the genus *Piroplasma*, but subsequently to a separate genus (1912). The parasites (Fig. XVIII) are of large size, usually rounded, occurring singly, in pairs, and occasionally in fours. The nucleus of the parasite is very large and rounded when at rest. Multiplication occurs by direct division of the nuclei, two daughter parasites resulting, which may in turn subdivide in a similar manner.

*Nicollia quadrigemina* (Nicolle, 1907), found in the gundi (*Ctenodactylus gundi*)—a rodent—in Tunisia by Nicolle, and referred by him to the genus *Piroplasma*; but it differs markedly from the members of this or any other genus, and a new genus was therefore founded for it by me in 1908. The parasites (Fig. XIX) are oval or piriform, are commonly grouped in fours, often in a fan-like manner, and show distinct binuclearity.

I am not clear as to the position of a considerable number of parasites in different animals and which have been referred to the genera *Piroplasma*, *Theileria*, *Achromaticus* and *Microsoma* by various authors. These parasites require further study before they can be definitely classed.

## TREATMENT AND PREVENTION.

In concluding, I must mention the subjects of treatment and prevention. The only drug hitherto discovered which exerts an influence on some of the parasites I have described

is trypanblue,<sup>3</sup> a dye which is administered intravenously in preference to subcutaneously in 1-1.5 per cent aqueous solution. A dose of 5-10 cc. is curative for dogs suffering from *Piroplasma canis* infection, and the drug is being used to-day in many parts of Africa where it was previously impossible to keep dogs. Trypanblue exerts the same effect on cattle and horses suffering from *P. bovis* and *P. caballi* infection; it has proved of value in practice in the treatment of horses and, apparently, of cattle, the dose being 100-150 cc. of the solution.

Trypanblue has no effect upon the parasites of East Coast Fever, and I have no satisfactory records of its having been tried upon the other parasites I have described.

Under the influence of trypanblue (Fig. XX) *Piroplasma* rapidly degenerates and the parasites can no longer be discovered microscopically in the blood. The fever and hæmoglobinuria cease, and the animals recover from the other clinical manifestations of piroplasmosis. (Compare Figs. XXI and

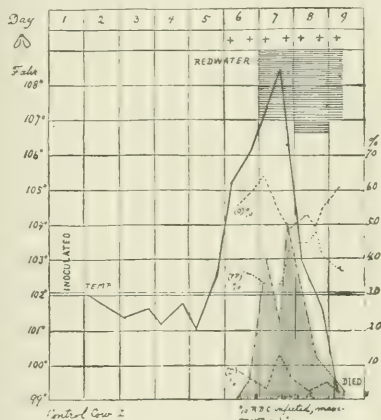


FIG. XXI.—Chart showing the course of events in an *unretarded* cow which died of redwater on the morning of the 9th day after inoculation with virulent blood. The presence of parasites (microscopically) in the blood is indicated by + marks on days 6-9; the intensity of the hæmoglobinuria is indicated by the amount of horizontal shading above, whilst the vertical shading below indicates the percentage of *P. bovis*-infected corpuscles. (Control Cow I. Nuttall and Hadwen, 1909.)

XXII). The animals continue, however, to harbor the parasites in their blood for years, as can be shown by inoculation into clean animals; in other words, the animals recover in the vast majority of cases from the acute disease, and, especially in dogs, are "salted" like the animals that recover in nature. Whereas untreated dogs usually die, the treated animals usually recover.

I may note that the inoculation of cattle is commonly employed with the object of obtaining "salted" animals, which are, naturally, more valuable than the "unsalted," in that they resist reinfection when exposed in endemic areas.

The efforts at prevention have been directed against the

<sup>5</sup> Nuttall & Hadwen (1909).

ticks which transmit the parasites and their transportation from place to place by their hosts. They consist in the use of dips, most of which contain arsenic, in which the animals, especially cattle, are immersed at intervals of a few days or a week or more. Where there are no forests to be endangered, the burning of the dry surface vegetation has been found of some use in destroying the ticks which infest the pasture lands, and, finally, the removal of cattle for a period from infested

pastures leading to the starving out of the ticks (especially *Boophilus*) has been found of use.

The preventive measures have to be based upon a knowledge of the life-histories of the ticks which transmit the parasites, and where they have been feasible and have been carried out intelligently they have been of great benefit, large tracts of country in the United States, Australia and Africa having been rendered almost tick-free by these measures.

## ENTEROGENOUS MESENTERIC CYSTS.

By ROBERT T. MILLER, JR., M. D.,

Surgeon to St. Francis Hospital, Pittsburgh, Pa.

Until recent years the subject of mesenteric cysts has been notable chiefly for the obscurity surrounding it. There have been numerous contributions made within the past 13 years, however, and while our knowledge is still not comprehensive, yet to-day we possess much more information concerning these curious tumors than is generally appreciated. The historical aspect of the subject was well presented by Moynihan<sup>1</sup> in 1897. In 1900 Dowd<sup>2</sup> published a notable paper which merited the wide recognition accorded it; this article has been largely responsible for the active interest in the general subject shown in the past 12 years, for it was an original contribution, and, in addition, stimulated several investigators into decidedly productive efforts. Owing to the many different captions under which the subject is discussed, it is practically impossible to conclude a review of the literature with certainty of completeness; it will suffice perhaps to say that with the help of the *Index Medicus* and *Hildebrandt*<sup>3</sup> it has been possible to study more than 100 papers appearing since 1900; the most notable are those by Colmers,<sup>4</sup> Terrier and Lecene,<sup>5</sup> Lewis and Thyng,<sup>6</sup> Niosi<sup>7</sup> and Bauer.<sup>8</sup> A detailed presentation of a single case is of value, in view of the following facts concerning mesenteric cysts, viz: there is wide difference of opinion as to their genesis; a positive diagnosis has probably never been made before operation or autopsy; and their surgical significance is almost universally ignored. In a summary of 35 cases Colmers found a mortality of 35 per cent, and yet our text-books accord the condition very scant notice.

The following case was referred to the surgical clinic of St. Francis Hospital from the Department of Obstetrics of the University of Pittsburgh, by Professor Charles Ziegler:

Intestinal obstruction, due to a congenital enterogenous mesenteric cyst. Operation on the abdomen. Recovery.

F. F. (No. 1493) female, 4 days old. Admitted September 28, 1912. Complaint: Vomiting and absolute constipation since birth. The patient is the last of thirteen children, all of whom, together with mother and father, are alive and well. Labor was neither prolonged nor difficult, no forceps being used. The baby has not retained any nourishment since birth; she has vomited everything taken, the vomitus being greenish-black in appearance. The bowels have not moved since birth. There has been no stain on the napkin.

*Examination.*—The baby is evidently exceedingly ill. When undisturbed she cries at intervals in a thin weak voice as though suffering paroxysms of pain. There is marked cyanosis of the face and hands. The skin is dry and wrinkled everywhere, but espe-

cially so over the extremities. The facial expression is pinched and drawn and the legs and arms are moved but little and that weakly; the picture suggests exhaustion due to suffering of some duration. The stump of the umbilical cord is still present with a small drop of purulent discharge at its base. The abdomen is symmetrical and not unusually distended. There is no visible peristalsis. Palpation causes the child to cry constantly and is unsatisfactory. Muscle spasm cannot be definitely recognized. No mass is palpated. The abdomen is generally tympanitic; there is no dullness in the flanks. On rectal examination the little finger can be inserted its full length and encounters no obstruction or mass. There is no blood or meconium on the examining finger. Temperature: 97° F. per rectum.

*Diagnosis.*—Intestinal obstruction, cause unknown.

As a long ambulance trip was possibly accountable in part for the child's poor condition, active efforts to raise her body temperature were made during the preparation for the operation.

*Operation.*—Under chloroform anæsthesia a right rectus incision was made. On opening the peritoneum there was seen both dilated and collapsed cyanotic loops of small bowel. Digital exploration revealed in the right flank just below the level of the umbilicus a freely movable mass which was easily brought up into the incision. This proved to be an intra-mesenteric tumor roughly oval, about 4 cm. long in its greatest diameter, and quite firm; over the dome of the mass and in very close relation to it there coursed a loop of small bowel, evidently about the level of the jejunum. This loop was flattened out into a thin and relatively wide band by the pressure of the subjacent tumor. There was a volvulus of the mass and affected sector of the bowel of rather more than 180 degrees in the direction of the hands of a clock, causing complete intestinal obstruction; the afferent bowel was greatly dilated and the efferent bowel quite collapsed. After reduction of the volvulus a circumferential area of pressure necrosis with a minute perforation was found on that portion of the afferent loop which had been drawn into the volvulus; in a limited area about the pressure ring the peritoneum was lusterless and in places there was a delicate deposit of fibrin. Cultures were taken from this area. The patient's condition urgently demanded haste, but a rapid enterostomy was not feasible since the obstruction was evidently high in the jejunum and drainage of the bowel at this point would have resulted in prompt starvation of a very weak patient. Immediate and permanent restoration of the continuity of the bowel seemed, however, imperative and accordingly a typical resection and lateral anastomosis were hurriedly made and the abdomen closed. The baby's condition seemed about as good as before operation.

When put to the breast shortly after the operation the patient seemed too weak to nurse, and though she retained milk given with a medicine dropper, she grew gradually weaker and died five hours later.

From the autopsy notes it will suffice to abstract the following pertinent points:

On opening the peritoneum it was seen to contain a considerable amount of clotted blood, which was present in all parts of the abdominal cavity. No evidence of an inflammatory reaction on the peritoneum could be observed. The stomach was dilated by gas, but was otherwise empty. The duodenum and upper part of the jejunum were markedly distended and dark in color. The distension extended down to the point of anastomosis, viz.: about 10 cm. from the pylorus. The suture line in the bowel was intact, as the intestinal contents could not be squeezed out. Below this point the entire bowel was collapsed. The autopsy was quite negative aside from the above findings. *B. coli* grew in pure culture in the inoculations made from the region about the perforation of the bowel.

The tissue removed at operation proved of great interest. The specimen consists of a loop of small bowel approximately 8 cm. in length, within whose mesentery there is a mass, roughly egg-shaped, measuring 4 cm. in its long axis and 3 cm. in its transverse axis. The mass lies between the mesenteric leaflets in close relation to the bowel, but projects much more upon one mesenteric aspect than the other in such a manner as to cause the mesenteric leaflets to join in a line which runs diagonally across one lateral aspect of the mass, as shown in the illustration. Over the surface of the mass course many rather large vessels. For a distance of 4.5 cm. the bowel is greatly compressed by the subjacent mass being flattened out into a ribbon-like band 1.5 cm. across at its widest point. On the afferent loop at a distance of 1 cm. from the mass there is a necrotic area, which has divided the bowel completely, with the exception of the peritoneum, in one-half of the circumference. The afferent loop is greatly dilated, measuring 4 cm. in diameter; the efferent loop is collapsed, measuring .6 cm. in diameter. The mass is regular in outline and its surface smooth; it is uniform in consistency, rather hard, but definitely fluctuant. On section it is seen to be a simple cyst, from which escapes a whitish mucoid fluid. The wall of the cyst varies in thickness from 1.2 mm. to 2.7 mm. The interior presents a smooth regular surface, grayish-white in color, and in places showing delicate parallel ridges running in a plane at right angles to the long axis of the cyst. That portion of the bowel which courses over the tightly distended cyst has been so stretched in width that its lumen is represented by a mere slit, crescentic in form; in this region the wall of the bowel and the wall of the cyst are blended into one structure which forms a partition between the two lumina. There is no communication between the bowel and the cyst.

Sections cut from the cyst wall at various points show a very regular histological arrangement. The cyst is lined by a single layer of epithelial cells resting upon a tissue layer analogous to submucosa; the next layer consists of smooth muscle whose internal half is cut in cross sections and whose external half is cut longitudinally. Beneath the peritoneum there is at places a layer consisting of many fine blood vessels held in a loose connective tissue stroma.

The lining epithelium consists of a single layer of high columnar cells whose protoplasm stains fairly well and whose nuclei are arranged uniformly at the base of the cells. Over the major portion of the cyst wall these cells are set closely together and thrown up into well-developed villi which have a connective tissue stroma and contain uniformly a capillary vessel. The villi reach their maximum size and frequency at a point on the cyst wall quite distant from the bowel; as the bowel wall is approached they gradually decrease in height and number and finally disappear, while the epithelial cells, markedly decreased in size, assume the low columnar type, which in turn changes to the cuboidal type just before the bowel wall is reached. Over that portion of the cyst wall subjacent to the lumen of the bowel the epithelium is quite flattened out. An occasional goblet cell is encountered. No

ciliated cells are seen. Nasse\* reports almost the same epithelial arrangement in an enterogenous mesenteric cyst excised on the 6th day of life under circumstances quite similar to those in my case.

Beneath the epithelium is a layer of loosely arranged connective tissue stroma enclosing blood vessels and numerous gland-like structures whose tubules are lined by epithelium quite similar to that on the surface. This layer, which resembles the submucosa, is well marked in the region where the villi are best developed, but gradually thins out as the bowel wall is approached; directly subjacent to the lumen of the bowel this layer is represented merely by a few connective tissue fibers. Throughout the entire cyst wall the two muscle layers are well developed and sharply differentiated, the one always being arranged at right angles to the other. As the bowel is approached the inner layer splits into two portions which ensheath the bowel and are continuous with its inner circular muscle layer. The external layer of muscle in the cyst wall remains intact and is directly continuous with the external longitudinal muscle of the bowel, thus forming a muscular envelope common to them both.

Apart from its structure as described above the bowel presents the usual appearance of the upper jejunum, viz.: numerous well-developed villi, with high columnar epithelium, and many goblet cells resting upon atypical submucosa. However, the structure alters as the cyst wall is approached; the villi disappear rather abruptly, and the high columnar changes to cuboidal epithelium, which lines perhaps one-fifth of the circumference of the lumen, and rests upon a submucosa almost devoid of secreting glands.

With overdistension of the cyst its wall will give at the weakest point, viz.: that portion acting as a septum between the lumina of the bowel and the cyst, since here there are lacking the whole external and one-half of the internal muscular layers of the cyst wall. Stretching of this septum accounts satisfactorily for the tissue changes occurring in both the cyst and the bowel at this point.

To summarize: The specimen consists of an intra-mesenteric cyst whose wall is, in part, directly continuous with that of the jejunum and whose histological structure resembles closely that of the adjoining portion of the bowel. Its structure and arrangement point directly to an enterogenous origin by a process of sequestration during embryonic life.

The genesis of mesenteric cysts was a very obscure subject until rather recent years. The ideas of the older pathologists were indefinite; such cysts were attributed variously to lymph stasis, with resultant dilatation of a lymphatic gland or vessel, and to cystic degeneration of a lipoma or of tuberculous glands. Dowd's article in 1900 aroused renewed interest in this subject, and recent work has resulted in a very considerable increase in our knowledge, though even now there is not a general agreement of opinion among the different investigators in this field. For instance, Dowd believes all mesenteric cysts to be of embryonic origin, while Niosi, in an excellent paper, states his belief that about one-half of all mesenteric cysts are acquired and places the so-called lymphatic and chylous cysts in this group. Klemm,\* on the other hand, finds the wall of lymphatic mesenteric cysts to be made up wholly of those cells which arise from the mesoderm, and argues that these cysts are neoplasms developing from misplaced or sequestered portions of mesodermic tissue, and hence form a group of tumors of embryonic origin for which he proposes the name of mesodermoids by way of analogy to that group of tumors which are now called dermoids. Arguments based on cellular structure must take into account the possibility of histological alterations in the wall of a cyst, for such changes could readily



obscure the picture; inflammation can substitute scar tissue for any other tissue. Conclusions based upon the character of the cyst contents can hardly be considered final, for, as Dowd has suggested, the fluid that collects in a preformed cyst is probably a mere matter of chance, whether lymph, chyle or blood from a ruptured mural vessel.

The state of our knowledge up to 1897 is perhaps best represented by Moynihan's classification of mesenteric cysts which appeared in that year, viz: 1, serous; 2, chylous; 3, hydatid; 4, blood; 5, dermoid; 6, cystic malignant disease; be it noted that only one group in this list suggests an embryonic origin. In 1900 Dowd successfully removed from the transverse mesocolon of an adult woman a cyst which closely resembled in detail a multilocular ovarian cystoma. The ovaries of this patient seemed normal on palpation. In presenting this case Dowd pointed out the close anatomical relationship existing in embryonic life between the Wolffian body or germinal epithelium and the root of the mesentery, and suggested the possibility of the sequestration from the germinal epithelium of a group of cells which might be displaced by the subsequent growth of the individual in such a way as to take up an intramesenteric position; later on, perhaps during the adult life, such a sequestrum from the germinal epithelium might develop into a tumor similar to the one he removed. Going further, he suggests that small portions of the developing gut may be similarly sequestered, to lie perhaps between the leaves of the mesentery and later develop into a cyst. He suggests as a classification of mesenteric cysts the following, viz: 1, embryonic; 2, hydatid; and, 3, cystic malignant disease. The emphasis he laid on the probable embryonic origin of a large number of mesenteric cysts represents a decided advance in our knowledge of this subject. Since Dowd's paper this idea has been repeatedly emphasized and elaborated; in a lengthy study, in 1907, Niosi, presented what is probably our best working classification of mesenteric cysts of embryonic origin, viz:

1. Cysts of intestinal origin:

- (a) By sequestration from the bowel occurring during development.
- (b) From Meckel's diverticulum when it arises from the concave side of the bowel [or acquires an intramesenteric position]. (The portion in brackets is added by the author.)

2. Dermoid cysts.

- 3. Cysts arising from retroperitoneal organs; viz: urogenital organs (germinal epithelium, ovary, Wolffian body, Mullerian duct).

The idea that a portion of an embryonic tissue or organ may become sequestered and still continue to develop, though usually in an anomalous manner, is a familiar one. Bauer credits Verneuil and Remak with the first proposal of the idea, while quoting Ribbert's "expression of the theory as the best. A free rendering of this passage from Ribbert is perhaps not superfluous: "Epithelial cysts may be formed not only as a result of trauma, but also by abnormal development; irregular growth may cause a change of position or a changed relation-

ship without actual change of position; or, again, epithelial structures which should coalesce fail to do so, or finally those which should decrease in size or disappear entirely retain their maximum dimensions. A group of epithelial cells with its connective tissue support is rendered more or less independent in growth by either of these processes and thenceforth develops as a cyst whose lumen is constantly enlarged by the retention of its own secretion and desquamated epithelium, although this increase in size is usually extremely slow and scarcely noticeable." When suggesting this process to explain the enterogenous origin of certain mesenteric cysts, Dowd argued by analogy, instancing the comparative frequency with which atypical development results in an accessory thyroid, spleen, or pancreas. The actual process of sequestration from the developing gut was not observed until 1908, when there appeared a report from Lewis and Thyng in which they describe the "regular occurrence of intestinal diverticula in embryos of the pig, rabbit and man." Previous to this time Lewis had discovered a "knob-like outpocketing of the intestinal epithelium a short distance beyond the pancreas" in a rabbit embryo, while Thyng had found a similar structure in a human embryo of 13.6 mm. and had interpreted it as an accessory pancreas. During further investigations, however, it was found that in the development of the small bowel of the embryos mentioned there always occurs a series of "knob-like intestinal diverticula," which appear earliest upon the proximal portion of the small bowel, together with the "cystic and bile ducts." In older embryos these structures were found in greater numbers on the distal portion of the small bowel; none were found on the large bowel, but the authors considered their presence here quite possible in more advanced embryos.

These diverticula consist of downgrowths of the intestinal epithelium which may terminate in the muscular coat of the bowel or may extend quite through the bowel wall to form knob-like projections. "They usually degenerate and disappear," but sometimes their continuity with the intestinal epithelium is destroyed and they persist as minute epithelial cysts or solid nests of epithelial cells lying in the muscle, or upon or near the bowel. One drawing shows such a cyst lying in the mesentery and in contact with the muscle of the duodenum in a pig embryo of 20 mm. Speaking in a later paper of the occurrence of duodenal diverticula in the adult, Lewis "suggests the possibility of their congenital origin," "although apparently no case has yet been recorded at birth," and, in discussing cysts, reference is again made to the embryonic mesenteric cyst just cited, with the suggestion that "it is possible that certain of the congenital intra-mesenteric cysts have a similar origin." The occurrence of these diverticula and cysts is not limited to the mesenteric border; when occurring on the convex border they exhibit changes in shape and size which suggest an alteration due to the rapid growth of this portion of the bowel. It may be that this relatively rapid growth causes the much more frequent disappearance of those so situated than of those lying in the mesentery.

Lewis and Thyng have thus established the fact that the formation of diverticula and cysts is a regular occurrence in the embryonic development of the gut. There can be scarcely

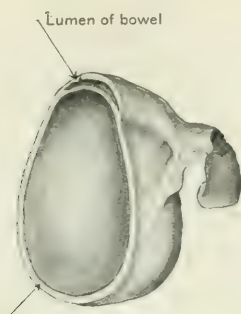


FIG. 1.—Cross section showing the compression of the bowel by the tense cyst.

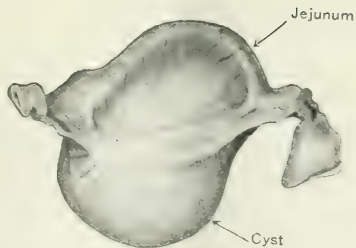


FIG. 2.—Cross section showing the compression of the bowel by the tense cyst.

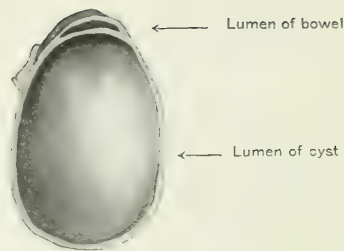


FIG. 3.—Cross section showing the compression of the bowel by the tense cyst.

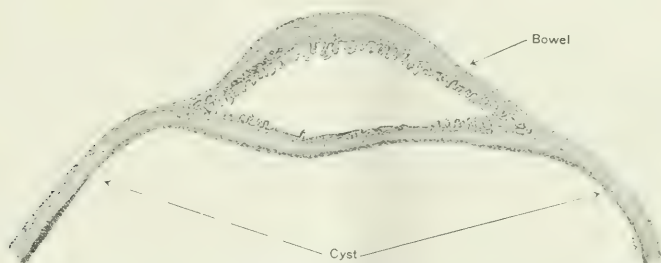


FIG. 4.—Microscopic section of the bowel and adjoining portions of the cyst wall. Note the blending of the walls of the two structures.

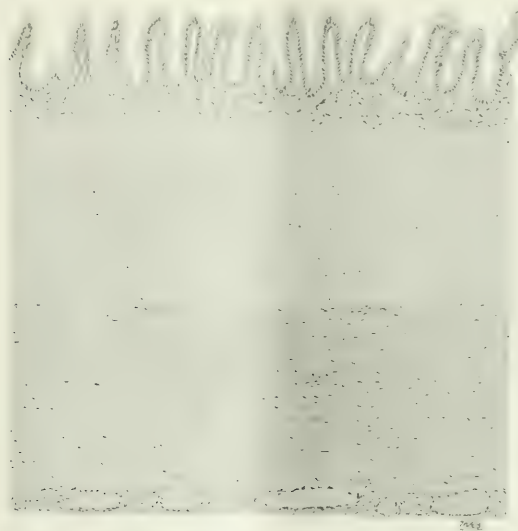


FIG. 5.—Microscopic section from that portion of the cyst wall farthest distant from the bowel. Note the almost exact similarity to the structure of the adjoining gut.





a doubt that such a cyst may occasionally persist to be recognized after birth as a "mesenteric cyst." The case which I have reported above seems certainly to belong to this group.

While the findings of Lewis and Thyng account for a certain number of mesenteric cysts, there is general agreement among those who have studied this question that most juxta-intestinal cysts, even when intramesenteric in position, have their origin in the vitelline or omphalo-mesenteric duct or in Meckel's diverticulum. By the end of the fourth week of fetal life the connection between the mid-gut and the umbilical vesicle has narrowed down to a fine canal, the omphalo-mesenteric duct, which runs from the bowel to the region of the umbilicus. Normally this canal becomes obliterated at the beginning of the second fetal month; when it persists as a blind duct emptying into the bowel it is known as Meckel's diverticulum. Meckel's diverticulum is said by Colmers to occur in about 2 per cent of all autopsies, but we do not know how frequently there may persist traces of the omphalo-mesenteric duct so small as to escape notice, and we are therefore unable to say just what proportion of individuals are born with a structure capable of developing by distension and growth into a juxta-intestinal cyst. The usual position of Meckel's diverticulum "is 43 inches above the ileo-caecal valve, but it varies widely (11 to 120 inches); Lamb "found it on the duodenum 7 times, on the jejunum 14 times, and on the ileum 160 times, where in 91 cases it was less than 36 inches above the valve. Leichtenstern "believes that when the growth of the oral half of the mid-gut is delayed or fails most of the small bowel must develop from the aboral half, thus placing the omphalo-mesenteric duct and Meckel's diverticulum at a relatively high position on the small bowel, while an over-growth of the oral half of the mid-gut results in a relatively low position of the diverticulum; this explanation may suffice possibly to account for the wide variation in its position. The convex side of the bowel is usually described as the normal situation for Meckel's diverticulum, but it may simulate or possibly even occupy an intra-mesenteric situation. Roth "states that the diverticulum is sometimes not situated exactly on the convexity, but more to one side, and suggests that when this variation is marked and the attachment approaches the mesenteric border the diverticulum might become blended with the mesentery and simulate an intra-mesenteric position. Hennig "suggests that shrinkage of the mesentery of a laterally placed diverticulum might draw it down and into the mesentery. Colmers assumes that an intra-mesenteric position is possible, but offers no explanation, while Ruge is quoted by Bauer as regarding the concave side of the bowel as the normal situation for Meckel's diverticulum, though no reason is given for this view. Fitz "interpreted a case of double cæcum as the persistence of an omphalo-mesenteric duct which arose low in the bowel and occupied an intra-mesenteric position.

It is apparently established that Meckel's diverticulum or persistent remnants of the omphalo-mesenteric duct may give rise to a mesenteric or juxta-intestinal cyst along practically the entire course of the small bowel, though such an occurrence must be exceeding rare in the extreme upper limits of the bowel.

A mesenteric cyst of either of these two types (Lewis and Thyng's embryonic cysts and the omphalo-mesenteric duct) arises from the bowel whose structure it shares; such a cyst, when typical and unaltered by inflammation, presents certain features which are quite characteristic and easily recognized. The resemblance to the adjacent bowel may be little short of exact, in that there is found a mucosa with typical glands, goblet cells and ciliated cells, well-developed villi, a distinct submucosa, and two layers of smooth muscle placed at right angles to each other.

The picture, however, is usually not so clear. The widest variations from the typical are found in the epithelial lining of such cysts. Frequently the formation of villi is incomplete, their presence being merely suggested by more or less faintly marked rugæ or papillæ, or the lining may consist of a smooth epithelial surface which in no way suggests villi; it quite often happens that a single specimen exhibits all variations, as in the case described above, where intra-cystic pressure with stretching of the wall seemed to offer the simplest explanation. Secreting glands may be present in typical arrangement or may be represented merely by a suggestive grouping of the epithelial cells. Rarely there is nothing even suggesting a gland. The type of epithelial cell also varies widely. Quite commonly the predominant cell is high columnar, with goblet cells occurring more or less frequently; ciliated cells have also been found, but are not common. Kostlivy "found a jejunal mesenteric cyst lined by a single layer of ciliated cells, and cites from the literature the occurrence of a similar epithelium in three other enterogenous cysts, but one of which was mesenteric, however. It is interesting to note that Roth, who, in 1881, was the first to draw attention to enterogenous cysts, described one lined by ciliated epithelium.

There sometimes occurs an epithelium which is quite atypical, if the expression may be allowed; thus among 15 accurately described enterogenous cysts whose records I have studied there are two lined with stratified cuboidal, one with stratified ciliated, and nine with simple columnar epithelium, while three multilocular cysts, probably enterogenous in origin, are lined with a stratified epithelium. These variations from the type are readily explained by the embryological development of the gut. The stomach and small bowel both pass through an early stage when their epithelium is regularly stratified; during this period there may be in the stomach three layers of epithelial cells, while the duodenum of embryos of "30 to 60 days is normally more or less completely obliterated " "by epithelial proliferation. Kollman "states that the epithelium of the developing gastro-intestinal tract undergoes a regular progression from simple cuboidal to simple cylindrical to stratified cylindrical, from which finally develops the permanent layer of simple cylindrical epithelium, which is ciliated in the respiratory tract. The conditions governing the growth of a group of epithelial cells sequestered during embryonic life would be quite anomalous; such a sequestrum might preserve the characteristics shown by its parent at the time of separation or might undergo retrograde changes or possibly might approximate a normal development. On these facts

most observers of an atypical epithelial lining have based an explanation of their findings.

The wall of a typical enterogenous cyst shows two well-developed layers of smooth muscle running at right angles to each other as they do in the bowel wall; such a cyst is of comparatively frequent occurrence. Not infrequently, however, one or both layers are poorly developed and irregularly arranged, and sometimes only a few isolated muscle fibers can be found scattered through the wall. At first glance the presence of smooth-muscle fibers in the wall of a mesenteric cyst would seem to indicate that such a cyst had arisen from the bowel; the question, however, is not so simple. In addition to the smooth muscle of the bowel wall there is certainly one and possibly two other sources from which smooth-muscle fibers in the wall of a mesenteric cyst may be derived. In the mesentery itself there regularly occurs a certain amount of unstriated muscle, portions of which might perhaps become incorporated in the wall of a cyst. Secondly, if we accept Klemm's idea that lymphatic mesenteric cysts are neoplasms, arising from misplaced portions of the mesoblastic layer, so-called mesodermoids, then we must expect smooth-muscle cells to occur regularly in the wall of such cysts along with the cells of the other tissues derived from the mesoblast. On the other hand, it is held by some that the absence of muscle cells in a cyst wall does not exclude an enterogenous origin, since these cells may have been destroyed by inflammation and replaced by scar tissue; Colmers, for instance, believes that even when "degeneration has destroyed the anatomical picture suggesting an intestinal origin the diagnosis of enterogenous cyst is justified if there is no proof to the contrary." Such an extreme position as that of Colmers can scarcely be accepted. No universally applicable law can be formulated to cover this question. We can certainly and positively affirm the enterogenous origin of any mesenteric cyst whose wall shows a well-developed musculature with an anatomical arrangement similar to that in the bowel. When, however, the picture is not so definite, or we find only a scant distribution of unstriated muscle lacking the typical arrangement, or perhaps no muscle at all, then we must seek farther for proof of an enterogenous origin. As a rule, the character of the lining will determine this point, but there will inevitably be instances in which we will be unable to finally decide the question.

The regional occurrence of enterogenous mesenteric cysts is apparently more or less distinctive. Since 1900 28 such cysts have been reported whose description is clear enough to permit classification. Of these 28 cases, including my case, all occurred in the mesentery of the small bowel, 7 occurred in the mesojejunum, 9 in the mesoileum, and 12 are said to have occurred in the mesentery of the small bowel, and hence probably in the mesoileum, since a higher location would have excited comment. The fact that all of these cysts were situated in the mesentery of the small bowel is striking; it may be merely a coincidence, but, nevertheless, it is suggestive when compared with the fact that the embryonic intestinal diverticula described by Lewis and Thyng all occurred on the small bowel: Stengel<sup>1</sup> found 15 of 18 "enteroid cysts" to occur in the mesoileum and regards this position as characteristic.

In 22 cases the cyst was unilocular, in 4 multilocular, and in 2 cases there were multiple cysts; Deaver<sup>2</sup> describes the occurrence of a cluster of 4 cysts about the ileum, one being within and one resting upon the mesentery, the arrangement of the four being such as to produce partial obstruction. Von der Bogert<sup>3</sup> describes the occurrence of 13 cysts in the mesoileum, 12 of these being of rather small size. The relation of a mesenteric cyst to the bowel varies. The cyst may impinge upon the bowel directly from behind, so to speak, compressing it from its mesenteric toward its free border; usually, however, the cyst presents largely upon one side of the mesentery and may occupy a position quite at the side of the bowel. Not infrequently, as in my case, the cyst exercises enough pressure to cause a partial intestinal obstruction. Enterogenous cysts occur with much less frequency along the free edge of the bowel. In 2 of the above 28 cases the cyst was more or less pedunculated. During a hernia operation Broca<sup>4</sup> found the sac occupied by a non-adherent cyst which had its origin in the mesentery of the small bowel; the cyst was successfully enucleated and on examination its wall was found to contain smooth muscle. This case is apparently unique.

Concerning the size of such cysts little need be said. It is not infrequent to find a content of one or two liters or the cyst compared in size to an adult head, but as a rule enterogenous cysts do not seem to attain great size and are usually indefinitely described as "about the size of an egg."

Given two possible origins for enterogenous or enteroid or juxta-intestinal cysts, as they are variously styled, it would be of great interest to determine in each case whether the cyst represented the process of sequestration from the bowel, as described by Lewis and Thyng, or whether it developed from Meckel's diverticulum or the persistent remains of the omphalo-mesenteric duct. Manifestly this problem presents many difficulties and is often wholly impossible. There are certain general features, however, which may be pointed out. The intestinal diverticula and cysts described by Lewis and Thyng make their first appearance regularly in the upper bowel about the duodenum and jejunum, and, while the position of the vitelline duct and Meckel's diverticulum varies widely, yet its occurrence in the jejunum or duodenum is exceptional. It follows therefore that a situation along the extreme upper bowel argues for an origin by sequestration.

The process of sequestration occurs regularly at multiple points about the entire circumference of the bowel, while Meckel's diverticulum is a single structure. Multiple or multilocular cysts therefore suggest a sequestration origin, although it is obvious that by a process of subdivision a persistent vitelline duct might give rise to more than one cyst. Too much importance must not be attached to an intra-mesenteric position of the cyst, since it appears not at all unlikely that this position may be occupied frequently by Meckel's diverticulum. Bauer has pointed out that sequestration cysts are much older, genetically speaking, than those arising from the vitelline duct; this being the case, we would naturally find atypical variations in cell structure, notably of the epithelium, more generally present in cysts of the former type. A remarkable case reported by Ahrens<sup>5</sup> illustrates this point very well. There was

removed from a retroperitoneal position on the right side a four-liter cyst, which resembled grossly an hour-glass stomach, and 26 cm. of adjoining bowel. Histologically the cyst wall showed the typical structure of stomach and bowel from mucous membrane outward, except that the epithelium consisted variously of stratified and simple cubical, stratified ciliated, high columnar and flat cells. The fluid contained in the cyst was weakly acid and digested egg albumen on the addition of HCl. There were multiple ulcers in the pseudostomach. J. W. Hall<sup>21</sup> and Roegner<sup>22</sup> also report cases bearing on this point. All three cases are probably sequestration cysts.

Of the secondary pathological processes affecting enterogenous cysts it is interesting to note that both Bauer and Colmers call attention to the occurrence of tuberculous ulcers of the cyst wall as well as of adenoma, carcinoma and spindle cell sarcoma. Suppuration rarely occurs in true cysts, though it is not infrequent in diverticula, structures whose genesis may be similar to that of the cysts and which may be readily confused with cysts.

The fact that a cyst of the mesentery has never been positively diagnosed before operation or autopsy is conclusive evidence that distinctive signs and symptoms do not exist or have escaped recognition. In considering enterogenous mesenteric cysts we may conveniently recognize two clinical divisions; the first group, about 50 per cent of the cases, includes those patients with acute complications, which are fatal unless given prompt surgical treatment, and the second group those whose symptoms are never urgent. This division is suggested because a rather large number suffer acute intestinal obstruction; and with such symptoms many mesenteric cysts have been chance findings during operation or autopsy. In this group enterogenous cysts appear in numbers disproportionately great as compared to other cysts of the mesentery; thus in 17 cases of enterogenous cysts with full histories we find acute obstruction 8 times or in about 50 per cent of the cases and usually in early life. Among 24 enterogenous cysts (including the above 17) 13 gave symptoms leading to surgical interference during the first ten years of life. Of these 13 cases 3 occurred in the first year, 3 in the third to fifth years, and 7 in the fifth to tenth years. My case was operated upon on the fourth day of life. Nasse reports operation on the sixth day. These are the only cases I find showing intestinal obstruction immediately after birth. Complete intestinal obstruction is usually due to volvulus. The explanation of this fact is not far to seek. Enterogenous cysts are commonly situated close to the bowel and not infrequently partially occlude its lumen; above the point of obstruction there results a compensatory hypertrophy of the muscle and exaggerated peristalsis. The size of the cyst is generally not extreme, being frequently compared to a hen's or goose's egg, but it is filled with fluid and is relatively heavy; thus we may roughly compare the cyst and adjacent sector of bowel to a suspended weight which is peculiarly liable to torsion, the power necessary to cause such torsion being supplied in part by the exaggerated peristalsis above the cyst. Among 35 cases of enterogenous cysts of the bowel or mesentery which Colmers collected, 19 required surgical treatment; 8 which were not operated upon died with symptoms of intestinal

obstruction or peritonitis, and of eleven operative cases 4 died, giving a grouped mortality of 12 cases or 35 per cent. He records the fact that in no case was a correct diagnosis made before operation. It thus appears that about one-half of all enterogenous mesenteric cysts cause acute intestinal obstruction, generally a volvulus, and that this calamity frequently occurs during the first decade. There is evident a striking similarity to intussusception in symptomatology, years of incidence, and obscurity of diagnosis, which urges caution in too "conservatively" withholding operation from a case of ileus in early life in the hope that a supposed intussusception will be reduced.

The remaining half of the cases, the latent cases, are not uniform in either symptoms or signs. There is frequently noted a sense of abdominal fullness, pressure or dragging; there is often a visible tumor or abdominal enlargement. Abdominal pain is quite common, but of no characteristic type. In only one instance was it associated with diarrhoea. Many cases in this group, perhaps most of them, give a history of mild recurrent attacks of partial intestinal obstruction.

The physical signs of a mesenteric cyst may be very definite, but are not pathognomonic. The typical case shows a freely movable, globular, fluctuant mass, varying in size up to that of the adult head, situated in any one of the four quadrants of the abdomen, and capable of being manipulated through a very wide range of motion. This last point is usually emphasized; it is sometimes possible to move such a tumor over the entire abdomen. These are simply the signs of any pedunculated cyst within the abdomen and are found in certain pathological conditions of the ovary, gall-bladder and kidney as well. In an instance, observed by the writer, a congenital occlusion of the ureter had converted the kidney into a large cyst, which answered rather accurately to the signs just enumerated. On percussion of a typical cyst one may find an area of flatness surrounded by a zone of tympany, a sign which is frequently referred to as important; judging from the records, however, this is by no means a constant feature. As a matter of fact, a perusal of the reported cases discloses so great a discrepancy between the signs actually observed and the so-called "typical" signs that one suspects imagination of having played a large part in the declaration of the latter. The fact that a correct diagnosis seems never to have been made needs no comment. A history and physical signs which conform in a general way to those which have been briefly presented above may suggest a mesenteric cyst very strongly, but an absolute diagnosis before operation or autopsy cannot be made.

The treatment of enterogenous mesenteric cysts may be covered in a few words. In the group of acute cases one is dealing always with intestinal obstruction or peritonitis and the therapy must be directed toward these conditions primarily; the operation is an emergency. In the second group, viz: the latent cases, the operation is an elective one and choice is to be made between drainage, enucleation and resection. Drainage is attended by a very low primary mortality, but is apt to result in a persistent sinus, which will ultimately require excision and, hence, is not altogether desirable. Without differentiating the type of cyst dealt with, Coley<sup>23</sup> has



estimated the mortality following drainage at 6 per cent; this probably includes some deaths due to complications and seems a very high rate. Enucleation was done 10 times without a death in 16 cases of my series. This is undoubtedly the procedure of choice when it is feasible, but conditions may render it impracticable. The cyst may be part and parcel of the intestinal wall, as in my case, where it would have been impossible to enucleate without opening the gut. Enucleation of a cyst or multiple cysts may do irreparable damage to the circulation of the bowel, enforcing resection. Dense adhesions may render enucleation impossible without tearing the bowel. The cyst may occupy an intra-intestinal position, as in several reported cases, near the ileo-cæcal valve and even be drawn into the cæcum, simulating an intussusception; in such circumstances the bowel must be opened to expose the cyst. These conditions among others may compel resection. In 5 cases of resection in my series there were 3 deaths, a mortality of 60 per cent. So high a mortality is due partly to the serious condition of most of these patients, of which my case is an excellent example, but the figures serve in a general way to emphasize the relative safety of enucleation of the cyst as compared to resection of the bowel. Undoubtedly the best treatment is enucleation when it can be done without seriously injuring or opening the bowel.

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## SALVARSAN IN PERNICIOUS ANÆMIA.<sup>1</sup>

By THOMAS R. BOGGS, M. D.,

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The scattered reports on the use of salvarsan in pernicious anæmia which have appeared in the last three years are conflicting and unsatisfactory. In many instances the observation was confined to a single case and the salvarsan was only

an accessory to the other standard therapeutic methods. As there has been repeated warning expressed in the literature against the use of salvarsan in this disease, it seems worth while to give a brief review of our own experience and some from the literature.

Bramwell's series of seven cases is an important contribu-

<sup>1</sup> Read at a meeting of the American Society for the Advancement of Clinical Investigation, Washington, D. C., May 5, 1913.

tion. With "cure" or favorable results in four cases, it is the most notable of the arguments for the use of salvarsan. Leede's five cases with unfavorable results are not nearly so instructive, as four of the cases were admittedly moribund when the drug was tried. The other case did seem to be injured by the two injections given.

Friedlander's case, refractory to Fowler's solution, was rapidly restored after two doses of salvarsan, followed by sodium cacodylate.

Through the courtesy of Professors Barker and Thayer, the writer has looked over the records of seven cases of pernicious anæmia, treated in part with salvarsan, at The Johns Hopkins Hospital. Of these, one received 0.3 gm. and died 48 hours later from pre-existing myocardial degeneration, without any reaction or any material change in the blood count. This patient was considered moribund on admission. Another case died 18 days after admission, receiving one dose of 0.2 gm. 11 days before death. There was no considerable reaction and no drop in the blood count of more than 200,000 cells. The remaining five showed improvement with initial drop in the blood count, never more than 200,000. As these cases also received sodium cacodylate or Fowler's solution, they are of value only as showing that the drug may be given to such patients without serious risk.

In our own experience at the Baltimore City Hospital we have had four cases, all of whom showed favorable reaction to the salvarsan in the regeneration of the blood and relief of the symptoms. One was a most remarkable apparent cure of a patient in his fifth relapse, who was quite unresponsive to Fowler's solution and only showed a very slight regeneration after a long period (four months) of sodium cacodylate injections. Under intravenous administration of salvarsan, in doses of 0.3 gm. every four weeks, he showed a steady rise in blood count. The red cells, in sixteen weeks, rose from 500,000 to 5,000,000, the hemoglobin from 23 per cent to 90 per cent, and the patient was well except for the mild degenerative changes in the spinal cord. He worked in the hospital for six months, as elevator man, and then left for outside employment and has been lost sight of. During the treatment the patient contracted tertian malaria and his blood count fell,

but rose again after quinine and the next dose of salvarsan. This patient had no history of syphilis, and also had a negative Wassermann reaction in serum and spinal fluid before any salvarsan was given.

Another case of pernicious anæmia, in which the nervous symptoms preceded the change in the blood picture by some months, was very responsive to salvarsan, his blood going from 1,100,000 to 3,400,000 red cells in twenty days after the first dose of 0.3 gm. intravenously, eventually reaching 4,800,000 with 85 per cent hemoglobin. This patient gave no history of syphilis and Wassermann reactions in serum and spinal fluid were quite negative.

In this case the patient seemed unable to sustain the higher level of blood formation and relapsed rather quickly, only to rise to approximately normal count again after two more doses. The blood picture, however, was never free from the qualitative changes of pernicious anæmia. After several rallies of this kind, covering a twelve-month, in which the subjective state was but little altered, the patient died of an intercurrent bronchopneumonia. Autopsy: typical changes of pernicious anæmia, with funicular degeneration in the cord.

The other two cases, both negative for syphilis, received but one injection each, and were greatly improved, with an average rise of 2,000,000 red cells when they left the hospital.

In our own cases and those from The Johns Hopkins Hospital there was, as a rule, a rather sharp febrile reaction, lasting six to twelve hours after each injection, in contrast to the very mild, or absent, reaction in syphilitics. All precautions were taken with regard to technic, *wasserfehler* and size of dose.

The results to date would certainly justify the further use of salvarsan in pernicious anæmia with special attention paid: (a) to the question of syphilis in the patient; (b) to the influence of salvarsan when given alone; (c) to the effect on arsenic refractory cases; and (d) permanency of the results.

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## ETIOLOGY OF ARTERIOSCLEROSIS.\*

By CHANNING FROTHINGHAM, JR., M. D., Boston, Mass.

Many different conceptions as to the nature of arteriosclerosis exist in the medical literature. To review them would be interesting, but outside the scope of this paper. In the chapter on diseases of the blood vessels, in his book which is about to be published, Dr. Mallory says: "Arteriosclerosis is the term applied to the more or less chronic lesions of the aorta and arteries or to the end products of these lesions. It is the end result of various toxic, nutritional, and infectious lesions involving the arterial system. It corresponds to sclerosis of the liver, kidney, and other organs. It is usually

of toxic origin, but may be the result of infection (syphilis). The two forms may be and often are combined. Disturbances of nutrition may play an important part, more particularly in the smaller vessels (kidney for example)." This description in my opinion covers most satisfactorily the various pathological conditions of a chronic character found in the blood vessels. It separates from arteriosclerosis the numerous acute pathological processes in the arteries and any physiological changes in thickness of the vessels at different ages which have often been reported.

Mallory, Klotz, and others emphasize the point that it is impossible to say from the end product of these arterial lesions

\* Read at a meeting of The Johns Hopkins Hospital Medical Society, May 5, 1913.

just what was the cause of the initial injury, except in certain rare types. Arteriosclerosis in any individual may be the result of an extensive injury to the arterial system produced in a short time, or simply the accumulation of a number of small injuries to the arteries scattered over a period of years. Therefore, in order to find the factors which produce arteriosclerosis, one must look for the etiological factors of any acute arterial lesions which will leave a scar on entirely or partially healing.

An important and as yet undecided question is whether the arterial wall adjacent to a healed or partially healed area suffers from disturbance of nutrition and therefore degenerates. If such is the case, a vicious sequence will be started after any permanent injury to the vessel wall, which will make the condition a progressive one. Before discussing the different agents that produce acute arterial lesions, I will present Dr. Mallory's classification of the different types of arterial degeneration and necrosis. His description is based upon the initial step in the process in each case, and it is evident that arteries respond in the same manner to a variety of toxic agents. The same active agent, however, may cause different types of lesions in the vessels of different organs. Hyaline formation is common in the spleen under a variety of acute and chronic conditions, but nothing similar occurs in the aorta. Also lesions that start the same may, as they progress, become quite different in appearance. In the larger arteries one layer may be involved without the others, but in the smaller all layers are usually involved together.

Dr. Mallory says, "Injury to the arterial wall manifests itself by two forms of retrograde change, by an accumulation of fat in the injured cells or by necrosis. These may be complicated by fibrine formation, hyaline transformation, or by the deposit of lime salts."

Any of the cells composing the vessel wall, fibroblasts, smooth muscle cells, or endothelial cells may be involved. Cells with fat in them may under improved conditions use up the fat and return to normal. A necrotic cell may call forth no reaction, if it dies suddenly and contains no fat. It will gradually be absorbed. Therefore these two types of acute lesion may heal without leaving a permanent scar.

Free fat from cells that have died or necrosis of any extent will call forth a cellular reaction of endothelial leucocytes, and if extensive enough polymorphonuclear neutrophils, and usually a proliferation of fibroblasts so that on healing a permanent scar remains. Occasionally there does not seem to be enough injury to call forth a marked reaction, and areas with considerable fatty degeneration persist with little attempt at repair. In other places the tissue probably is not able to completely recover, but remains in a state of degeneration with moderate reaction. In the distributing arteries necrosis may occur in the media entirely independent of the intima. In these cases fat and lime salts may be present without any reaction about them. Chronic and acute arterial lesions like all other lesions may be very irregularly and unaccountably distributed throughout the body.

I will now take up a list of the agents between which and the arterial lesion a direct relation seems to be fairly well

established, either by a study of autopsy material, animal experimentation, or clinical observation. Before the discovery of the *treponema pallida* it was a well recognized clinical observation that patients presenting a history of syphilis frequently showed evidence of arteriosclerosis. Fremont Smith reported a case of a boy of 12 years with severe general sclerosis which he felt was surely due to congenital syphilis. Recently the discovery of the spirochetæ of syphilis by Wright and Richardson and others as causative agents in lesions that leave a permanent scar in arteries proves conclusively that this organism plays a part in the cause of arteriosclerosis.

The tubercle bacillus may produce arterial lesions by extension from neighboring lesions, or by infection of the wall from the inside. Wooley recently reported such a case and referred to others. Of course such lesions would be rare and play little part, even if they healed, in causing a general sclerosis. In order to see if the tubercle bacillus had a soluble toxin which might produce a more general arterial lesion, I studied six fatal cases of tuberculosis under 25 years of age. Tissue from the spleen, aorta, and kidneys was examined. One of the cases, an infant under two years of age, showed no arterial lesions. The others in one or more organs showed lesions which would leave a permanent scar on healing. Of course it is impossible to say that these were due to the tubercle poison more than to metabolic poisons which might have arisen from the general weakened condition. This is especially difficult to decide since the character of the lesion would presumably be the same in either case.

The leprosy and glanders bacilli have been found in acute arterial lesions, but those diseases are so uncommon that they can play very little part in the cause of arteriosclerosis, and so I will only briefly mention them.

Flexner reported acute arteritis in typhoid fever. In two cases under 25 years of age I found slight degenerative lesions in the kidney and splenic arteries from which recovery was possible, and slight lesions of a permanent character in the aortæ. Here also the question justly may be raised as to whether there is any specific action from the typhoid toxin which causes these lesions. Experimentally Klotz claims some positive results in the aorta from injection of typhoid bacilli into rabbits. I could not produce any lesions from the injection of typhoid vaccines in guinea pigs. Clinically Thayer and Brush have found that a series of people who have had typhoid fever present more palpable radial arteries than a series of people who have not, who live in presumably the same circumstances. The direct evidence against the typhoid bacillus as a factor in the cause of arteriosclerosis is somewhat questionable.

Near the site of the diphtheria membrane I have found extensive necrosis of the vessel walls which will undoubtedly leave a permanent scar on healing. In looking for a generally distributed lesion in 10 cases under 25 years of age none were found in 3 cases under 2 years of age. In the other 7 cases the splenic vessels consistently showed a lesion which would leave a scar on healing, and the kidney and aorta occasionally did. Wiesel, in a study of the vessels in children dead of diphtheria, reports very general arterial lesions.



Experimentally Thérèse, Pernice, Boinet and Romary, and Klotz found lesions in the rabbit's aorta after injection of diphtheria toxin similar to arteriosclerosis in man. At the present time it is only fair to state that the relation between this type of disease in rabbits' aortae and the substances injected is not well established. My feeling is that for the present this type of arterial lesion in rabbits had better be considered as a spontaneous lesion and not the result of the substances injected. Recently I have produced an extensive lesion in some of the smaller vessels of the rabbit's kidney with diphtheria toxin which would undoubtedly leave a permanent scar on healing. Clinical evidence in regard to the relation of diphtheria toxin and arteriosclerosis is lacking.

In cases infected by any one of the group of bacteria including the pneumococcus, staphylococcus, streptococcus, and the diplococcus of acute articular rheumatism Wiesner, Wiesel, and Symnitzky have all reported evidence of arterial degeneration in those of young age. Mallory and others have found marked arterial necrosis with fibrin formation and cellular reaction scattered throughout the different organs in such cases. Out of 48 cases dying from acute infection I found in one or more organs such lesions in some of the arteries in 8 cases. In addition to these cases with the extensive localized lesion I studied 18 cases under 25 years of age infected with these organisms to see if there was any diffuse lesion attributable to their toxins. I found practically no lesions in children under 2 years of age. In the others there was some evidence of lesions in the arteries of the spleen and aorta which would produce a permanent change on healing, but very little in the kidneys. Saltykow, Crocq, Klotz, and others have obtained positive results in rabbits and guinea pigs with such toxins, but it seems to me necessary to have the work confirmed. By the injection of staphylococcus vaccine in young guinea pigs, I was able to keep them from being as large as the controls, but did not produce any arterial lesions. Clinically Thayer and Brush have found that the radial arteries of people, who have had these infections, especially rheumatism, are more readily palpable than those of controls. It is certain therefore that these infections may cause localized arterial lesions, but the evidence in regard to their causing diffuse arterial disease is lacking.

In poliomyelitis Robertson and Chesley have found local arterial degenerations in the spinal cord, and in influenza meningitis Rhea has reported a lesion in the meningeal vessels. There have been practically no other observations with these infective agents.

From these different findings it is evident that certain of the infections with organisms produce quite marked injury to arteries either by their presence or by the action of their concentrated toxins. These lesions are usually limited in their distribution. In addition many of the acute infections have associated with them more or less diffuse arterial lesions of a chronic type in one or more organs. As investigation continues along these lines it seems probable that more organisms producing infectious diseases will be found to produce arterial lesions.

Fremont Smith quotes many authors who have found e

tensive sclerosis in young people and fetuses without apparent cause. I studied the clinical histories of two cases of marked sclerosis, aged 22 and 16 years, in order to see if any light could be thrown on the cause from this source, but there was no evidence of any one particular cause that might have produced the condition.

The relation between non-infectious toxins and arteriosclerosis is clinically and pathologically more marked, but yet more difficult to prove, because it occurs chiefly in older people in whom other factors might well take a part. Foremost among the non-infectious toxins are either an excess of the normal products of metabolism, or abnormal elements produced by a disordered metabolism. One or both of these appear during the course of a chronic nephritis. That the poisons during a chronic nephritis produce lesions in the vessels of a permanent nature seems certain from the extent of involvement seen post mortem in patients with chronic nephritis, as compared with others from the same environment dead from other causes. I attempted, by having both kidneys removed from rabbits by Dr. Loder, to produce arterial lesions by uræmic poisoning. The animals lived long enough, about 2 days, for fatty changes to appear in the cells of several organs, but the blood vessels appeared normal. Clinically chronic nephritis cases show evidence of arteriosclerosis.

In chronic jaundice cases extensive fatty changes have been reported in the aorta which were so marked that a relationship between it and the bile seems justifiable. Dr. Minot and I endeavored to produce vascular changes in rabbits by the injection of bovine bile both intravenously and intraperitoneally. Although in some of the animals fatty changes were present in some of the parenchymatous cells no arterial lesions were obtained. Whether the fatty changes produced by bile go on to permanent arterial changes has not been definitely settled.

Clinically and at autopsy, cases of lead poisoning usually show extensive sclerosis of the arteries. They also usually show nephritis to some extent. It is therefore difficult to place the blame for a specific action upon the lead. I fed young rabbits lead acetate over a period of 2 to 3 weeks in such amounts that some died and others were killed while quite sick. These animals showed no arterial lesions.

In addition to the acute infectious toxins and organisms which may produce arteriosclerosis, must be mentioned, therefore, the poisonous products of metabolism remaining in the system due to faulty elimination. Lead also must be borne in mind as a probable etiological factor.

Whether cells wear out under perfectly normal conditions from old age is a question in regard to which there is no definite clinical, post mortem, or experimental proof. It must not be forgotten, however, as an etiological factor in the production of sclerosis of the arteries.

It would probably simplify the situation to stop here and omit from consideration any other possibilities as a cause for arteriosclerosis. It is impossible, however, not to mention some of the numerous agents accused of causing arteriosclerosis in the literature. These can be best grouped as toxic and non-toxic agents.

Of the toxic ones those receiving the most attention at the present are the poisons absorbed from the alimentary tract as a result of proteid decomposition. Metchnikoff has worked out a theory that some of the scleroses in organs and vessels met with in old age are the result of the absorption of indol, paracresol, etc. He reports some positive experimental results with the injection of paracresol, and Dratchinski reports arterial scleroses after injection of indol in animals. To me the work is not in the least convincing, and the application of these theories to man seems to be entirely theoretical, without a firm experimental, clinical, or pathological basis to stand upon.

Clinically the use of alcohol has been shown pretty suggestively by Thayer and Brush to be a factor in the cause of arteriosclerosis. Pathologically Cabot has offered some very convincing statistics to show that alcohol does not play any part in causing arteriosclerosis. Experimentally little has been done with alcohol in arterial work.

There has been evidence brought clinically against nicotine as an agent in producing arteriosclerosis. Hochwart of Vienna has written on the subject. Experimentally Adler and Hensel have had some positive results in rabbits. The direct proof that nicotine may cause arterial lesions in man is lacking.

Most of the writers on this subject speak of the relation between gout and arteriosclerosis although there is little pathological or experimental evidence to back it up.

The non-toxic factors mentioned as producing arteriosclerosis are heredity, changes in blood pressure, and overwork. Since arteriosclerosis is not a specific disease, but a summation of injuries from one or more sources, it is not clear to me how heredity can be looked upon as a cause of sclerosis except in that one person's vessels are less capable of withstanding infections and metabolic poisons than others. Such proof is exceedingly difficult to produce, as, to do so, it would be necessary to be able to measure the degree of virulence of the individual toxin. However, Osler, Brill and Libman, and others speak of the part heredity may play in this disease.

Changes of blood pressure have been held accountable for arteriosclerotic lesions. Romberg even mentions that emotions may cause arteriosclerosis by frequent oscillations of pressure. To study this point substances that either raise or lower blood pressure have been injected into animals. Foremost among them are adrenalin and nicotine. Clinically and from post mortem examinations there has been practically nothing in the way of direct evidence against the substances capable of changing blood pressure. Experimentally since the first report of Josue in 1903 adrenalin and other blood raising or lowering drugs have been administered chiefly to rabbits, and occasionally to other animals. Adler and Hensel have worked with nicotine. A great many positive results have been obtained. The question always comes up as to the relation between these results and the spontaneous disease in

rabbits' aorta. At the present it seems fair to state that there is no proof that such substances produce arterial changes of a permanent character in man.

In regard to overwork there has been practically no experimental study reported. Thayer and Fabyan have shown the pathological changes in the radial arteries from age and strain. It has been observed clinically that motormen who are on their feet a long time may show markedly sclerosed femoral arteries and blacksmiths may show more sclerosis in their right arms than in their left. Thayer and Brush have found the radials more palpable in those who indulge in heavy physical labor. Klotz considers progressive medial disease in the peripheral vessels the result of muscle fatigue and nutritional disturbance.

As one goes down the list of substances accused of producing arteriosclerosis the proof in support of the claims becomes less and less. It seems to me, therefore, that, until some more definite evidence is offered against any agent it is best to consider that the only causative factors in the production of arteriosclerosis are the products of normal or abnormal metabolism retained in the body through faulty elimination, and the acute infections. Justifiable suspicion, however, points towards a number of the factors mentioned above.

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# BULLETIN

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## AN EXPERIMENTAL AND CLINICAL STUDY OF THE VALUE OF PHENOLTETRACHLORPHTHALEIN AS A TEST FOR HEPATIC FUNCTION.

By L. G. ROWNTREE, M. D., S. H. HURWITZ, M. D., and A. L. BLOOMFIELD, M. D., Baltimore.

(From the Pharmacological Laboratory of The Johns Hopkins University and the Medical Clinic of The Johns Hopkins Hospital.)

In this investigation an effort has been made to determine whether the quantity of phenoltetrachlorphthalein excreted by the liver following its intravenous administration affords an index of the functional capacity of the liver. The specificity displayed by the liver in the excretion of this dye, which is analogous in every way to that exhibited by the kidney towards phenolsulphonephthalein, strongly suggests possibilities in this connection. Quantitative studies of the phthalein output in health and in liver diseases (clinical and experimental) have therefore been undertaken.

### THE FUNCTION OF THE LIVER IN HEALTH.

The liver plays an important rôle in the general nutrition of the body. No anatomical or functional differentiation of liver cells exists, all being identical as far as can be determined. Three functions of liver cells are definitely established: (1) The glycogenic function, relating to carbohydrate metabolism. This consists of (a) the conversion through enzymatic activity of monosaccharides (dextrose, levulose and galactose) brought to the liver cells by the blood, into glycogen, a polysaccharide closely related to starch; (b) the temporary storage of glycogen as such, until (c) the re-conversion of glycogen by liver enzymes into dextrose as need arises for sugar throughout the body. (2) The formation

of urea in relation to nitrogenous metabolism through the activity of the liver cells. This consists in the conversion of certain nitrogenous bodies ( $\text{NH}_3$ , amino acids, etc.) into urea, which in turn is carried to the kidneys, where it is excreted. (3) The formation of bile, which is in part an excretion carrying with it waste material and in part a secretion concerned in digestion, playing an important rôle, particularly in the absorption of fats.

Other functions are frequently ascribed to the liver. Their connection with it, however, is not so well established and they have not played so important a rôle in the studies of liver physiology. In this group must be considered the formation of fibrinogen and of antithrombin. Undoubtedly still other important functions exist of which at present little or nothing is known.

### THE FUNCTION OF THE LIVER IN DISEASE.

With the occurrence of disease in the liver, functional changes undoubtedly appear. Their character varies greatly with the nature of the underlying pathological processes at work. They can be associated with, or totally independent of, morphological changes, macroscopically or microscopically demonstrable. In most of the outspoken diseases of the liver, however, recognizable objective anatomical alterations occur,



such as enlargement or contraction, changes in consistency, etc. They may or may not be associated with evidence of portal obstruction, ascites, the development of enlarged collateral circulatory channels or of biliary obstruction—jaundice, bile in the urine, acholic stools, etc.

Through routine clinical histories and examinations, with a study of the urine and feces, the presence or absence of liver disease can be readily determined in most cases. Information concerning the severity of the disease and the extent of the involvement of liver function is, however, not so readily obtained. In certain liver affections symptoms either of an obstructive or toxic nature are ascribed to the liver changes. There is not, however, a well-defined symptom complex which can be accepted as the picture of hepatic insufficiency, such as exists, for instance, in relation to diseases of other viscera—the kidney, heart, suprarenals and thyroid. In other words, the clinical picture and anatomical changes, even when outspoken, do not furnish an accurate conception of the functional condition of the liver, nor do they furnish reliable criteria concerning the outcome of these functional changes.

In certain other diseases, concerning the etiology and physiological pathology of which no accurate knowledge exists, the liver is thought to be implicated. Information about hepatic function in these conditions is most desirable and necessary.

The unsatisfactory character of the information obtained through ordinary routine clinical studies is apparent to every thoughtful clinician. The desirability of broadening and deepening our acquaintance with the functional conditions present in disease is indicated by the existence of a large number of tests devised and introduced for this purpose.

#### THE IDEAL FUNCTIONAL TEST

A perfect conception of the status of liver function in disease presupposes an accurate knowledge of all the physiological functions of the liver in health and in disease. Do dissociated injuries to one function or set of functions exist without interference with other functions? If so, reliable quantitative tests for each set of activities is demanded. Our knowledge of liver physiology, however, is inadequate and much information, fundamental in nature, is needed before such tests can be devised.

It is worth while to consider what would constitute an ideal single test of total liver function. Is such a test possible? What could be justly demanded of it?

1. The test should indicate within narrow limits a constant amount of work performed by all normal livers under normal conditions.

2. It should indicate constant variations in function where constant abnormal conditions of either an experimental or clinical nature exist.

3. It should indicate functional alterations independent of the histological appearance.

4. It should afford an indication of the absolute work accomplished as well as the relation of this to the normal

standard under all conditions; that is, it should indicate correctly the degree of functional injury, thus carrying prognostic significance.

5. Where less than the minimal amount of liver capable of carrying on function is left free from disease or injury, corresponding lowering of function should be indicated.

6. Where all liver cells are diffusely involved, lowered function should be indicated, but where certain cells are injured while others take on, through compensatory activity, additional function, the total functional capacity alone should be indicated.

7. It should be applicable with as simple technic as possible, so as to be available for general use in all forms of liver injury.

8. It should be applicable without injury of any kind (local or general) to the patient and without placing the liver under any additional strain.

9. The method itself should be mathematically accurate.

10. Its results should be easy of interpretation.

11. Its results should not be subject to influence from involvement of any other organs or systems, except in so far as the liver function is secondarily affected; that is, the test should be specific for liver changes.

#### THE TESTS OF LIVER FUNCTION.

Numerous tests have been employed in the effort to determine the functional capacity of the liver in disease. They are mostly based upon the physiological functions of the liver and attempt quantitatively or qualitatively to determine its capacity along such lines.

#### THE CARBOHYDRATE TESTS.

The discovery of the glycogenic function of the liver in 1857 by Claude Bernard immediately stimulated extensive work in carbohydrate metabolism by physiologists, pathologists and clinicians. During the course of a rather heated controversy which waged in the German and French literature between 1875 and 1900 concerning the relationship of the liver to glycosuria after the administration of large amounts of carbohydrate, the idea of utilizing the sugars for testing hepatic function arose. The French school led by Roger,<sup>1</sup> Achard and Castaigne, Baylac<sup>2</sup> and Bierens de Haen<sup>3</sup> championed the sugars as tests of liver function, while the German school under the leadership of Quincke,<sup>4</sup> Frerichs, von Noorden,<sup>5</sup> Kraus and Ludwig,<sup>6</sup> Bloch,<sup>7</sup> and Müller, were unable to demonstrate any marked or constant reduction in sugar tolerance in cases of liver disease.

In a series of papers in 1893-1900 Strauss<sup>8</sup> established the view that the discrepancies in the results of these various workers could be explained by differences in the particular carbohydrate employed, together with differences in the amounts of sugar administered. He demonstrated that 100 gm. of dextrose in 500 cc. water given on an empty stomach gave rise to glycosuria in but two out of 38 cases of liver disease, whereas a considerable proportion of all

hepatopathies showed the presence of sugar in the urine following the administration of the same amount of cane sugar. He ascribed the difference to the presence of levulose in the cane sugar. He concluded that both cane sugar and dextrose were inapplicable, since there existed a mechanism other than that in the liver capable of metabolising them. He followed his criticism of this work by his levulose test, based on the work of Sachs,<sup>10</sup> which showed a constant decreased tolerance for levulose in liverless frogs.

#### STRAUSS' LEVULOSE TEST.

One hundred grams of levulose are administered on an empty stomach, and the urine voided during the following four hours tested by Trommer's and Seliwanoff's tests, by fermentation and polarization. The normal individual should tolerate 100 gm. levulose without glycosuria. The test came rapidly into wide use, the results differing with various workers. A contrast between the findings in health and disease, together with the attitude of various workers concerning the value of the test, is seen in the following table.

THE LEVULOSE TEST.

Author.	Normal livers.		Abnormal livers		Remarks.
	Cases.	Positive.	Cases.	Positive.	
Strauss <sup>8</sup> 9...	58	6	25	23	Test is of value.
Ferranini <sup>11</sup> .	..	..	16	15	Test preferable to glucose test, which showed only 10 positive.
Landsberg <sup>12</sup> .	7	4	21	9	He thinks that normally tolerance varies so much that test is of no importance.
Chajes <sup>13</sup> ....	21	2	..	..	He thinks that positive findings are rare in normals.
v. Halasz <sup>14</sup> ..	20	1	23	8	The 8 positive findings were in cirrhosis; considers it of value.
Hohlweg <sup>15</sup> ..	..	..	30	9	Ten cases were chronic passive congestion.
v. Frey <sup>16</sup> ....	..	..	26	14	Considering only those positive with more than 0.1 gm. sugar in urine.
Churchman <sup>17</sup>	38	9	12	10	Considers test unsatisfactory since neither a positive nor negative finding is conclusive.
Falk & Saxl <sup>18</sup>	..	..	351	259	Collected from literature.
Bruening <sup>19</sup> ..	..	..	30	27	Considered the test of value.

In reading the reports of most of these workers, difficulty is experienced in arriving at a conclusion concerning the value of the test in individual cases, since detailed clinical data and autopsy findings are not given. It appears, however, that the test is far from satisfactory and that much reliance from either a diagnostic or prognostic standpoint cannot be placed in its findings.

#### BAUER'S GALACTOSE TEST.

In 1906 Bauer<sup>20</sup> introduced galactose as a liver test. He administered 40 gm. in 400 to 500 cc. of tea on an empty stomach and determined quantitatively the amount of sugar

present in the urine voided in the next 4 to 5 hours. In severe catarrhal jaundice large amounts of galactose appeared in the urine, but as the condition improved the amount in the urine quickly diminished. The amount recovered was greater in catarrhal jaundice than in jaundice due to other causes (gall stones, cancer). He considers it a test of liver function in catarrhal jaundice. Bondi and König,<sup>21</sup> Riess and Jehn,<sup>22</sup> and Hirose<sup>23</sup> confirmed this, believing it to be of importance in this connection.

The work of Falk and Saxl,<sup>18</sup> v. Frey<sup>16</sup> and Hirose<sup>23</sup> shows that the results of the test are very inconstant in diseases of the liver other than catarrhal jaundice.

In general, the shortcomings and disadvantages of carbohydrate tests, as they have been utilized, might be summarized as follows: (1) The use of arbitrary amounts of sugar without consideration of the normal tolerance of the individual patient; (2) the difficulty of keeping the patient on a carbohydrate free or a carbohydrate constant diet at the time of the test; (3) the practical difficulties of administration (nausea, vomiting, diarrhoea); (4) the disregard of such complications as portal obstruction, autonomic nervous derangement and disturbances of internal secretions influencing carbohydrate metabolism.\*

#### UREA, AMINO ACID, AND AMMONIA NITROGEN.

Glaessner<sup>24</sup> showed in 1907 that in most instances of liver disease an unusually high excretion of amino acid N occurred and that the ratio of amino N to total N was also increased. Whereas normally he found the amino N constitutes only 0.2 to 0.4 per cent,† in pathological conditions of the liver it is decidedly higher, *e. g.*, secondary cancer of the liver 12.4 to 16.2 per cent, catarrhal jaundice 4.5 per cent, chronic alcoholic and fatty liver 6.9 to 8.33 per cent, luetic hepatitis 4.1 per cent, cirrhosis 3 to 13.4 per cent and in phosphorus liver 6 per cent. Falk and Hesky<sup>25</sup> showed that the urine of pregnant women contained increased amino acid N in 75 per cent of pregnancies. This they attributed to liver injury associated with pregnancy.

Falk and Saxl<sup>18</sup> have attempted further to follow the peptid N as well, determining both the amino and peptid N after feeding various nitrogenous foodstuffs to patients with normal and diseased livers. On feeding glycocoll to patients, they learned that diseased livers could not convert this amino acid into urea, but that it was excreted in part unchanged in

\* Strauss (Deutsche med. Wchnschr., 1903, xxxix, 1780), presents further evidence to establish the value of the levulose test, and insists upon the adoption of a constant amount of galactose (30 gm.) in utilizing Bauer's test in order that the finding of the other tests may be compared.

† Henriques<sup>26</sup> using Sorensen's formal titration method, states that the amino acid N in man on an ordinary mixed diet constitutes 2 per cent of the total N. Levene and Van Slyke<sup>27</sup> place the normal amino acid content of urine as 1 per cent to 2.8 per cent of the total N.

‡ Kober (J. Am. Chem. Soc., 1913, xxxv, 1567), utilizing his new method for determining amino N places the amino N at 2.7 to 3.1 of the total N.

the urine. The peptid nitrogen they found increased when the amino N was high.

In a second communication these authors divided the liver cases into four groups, giving the results as indicated in the literature.

GROUP I.—Comprising tumors, sarcoma, carcinoma, leukemia, amyloid disease, and chronic passive congestion. Normal amino and urea N values are encountered in sarcoma, leukemia, amyloid disease, and chronic passive congestion (Stadelmann). In carcinoma the urea N may be reduced while the amino N per cent is high.

GROUP II.—Consisting of various intoxications, *e. g.*: chloroform, phosphorus and alcohol; and febrile conditions, such as typhoid, scarlet fever, and pneumonia. The febrile diseases are associated with only slight diminution of urea N, while in the other conditions—phosphorus poisoning, for instance, the decrease is somewhat greater, 74 to 86 per cent (Münzer), 55 to 85 per cent (Sjöqvist) of the total N instead of the normal 91 per cent.

GROUP III (ICTERUS).—In 27 cases of catarrhal jaundice and cholelithiasis there was no appreciable reduction of urea N which remained 80 to 87 per cent of the total N (von Noorden), 85 per cent (Mörner and Sjöqvist). The amino N is occasionally increased 8.1 per cent (Mörner and Sjöqvist), 4.9 to 9.5 per cent (von Noorden). The amino and peptid N is increased 4.5 per cent (Glaessner), 4.6 per cent (Falk and Saxl).

GROUP IV (CIRRHOSIS).—The urea N is slightly decreased. The amino N is invariably increased to more than 0.5 gm. according to v. Frey. This he considers of tremendous importance, since only rarely is so high an amino acid N output found in other diseases of the liver. The ammonia N is also constantly increased.

There is found in severe liver involvement, therefore, increase in the amino acid, peptid and  $\text{NH}_3\text{N}$  at the expense of urea N.\*

#### UROBILINOGEN.

As early as 1892 the presence of urobilinogen in the urine was considered as indicative of disease of the liver by v. Jaksch.<sup>22</sup> The test consists simply in the qualitative determination of the presence of urobilinogen in the urine. Since Neubauer's<sup>23</sup> demonstration that Ehrlich's<sup>24</sup> p. dimethyl-amino-benzaldehyde test given by the urine in certain diseases is really a test for urobilinogen, this test is utilized. A few crystals of p. dimethyl-amino-benzaldehyd are added to a few cubic centimeters of urine, the mixture is shaken, and made definitely acid with HCl or acetic acid, whereupon an intense red color develops if urobilinogen be present.

Urobilinogen does not occur in health, the cycle in relation to bile pigments being as follows: Bile pigments are converted in the intestine into urobilinogen, which is absorbed, carried to the liver, and re-converted into ordinary bile pig-

ments. The diseased liver cells having lost, to a greater or less extent, the capacity for reconversion, the urobilinogen, after absorption, continues to circulate and eventually finds its way into the urine. Urobilinogenuria, therefore, indicates functional incapacity of liver cells.

Münzer<sup>25</sup> states that urobilinogen appears in the urine in atrophic cirrhosis; Münzer and Bloch,<sup>26</sup> and also Fischer,<sup>27</sup> find that it appears in acute catarrhal jaundice prior to the appearance of the icterus, and in acute diseases associated with liver involvement (typhoid and pneumonia with acute hepatic parenchymatous changes). According to Münzer, urobilinogenuria is not present in pseudo-cirrhosis (Pick's disease), or in chronic passive congestion of the liver, where true liver disease is absent. He, therefore, considers the test of importance in differentiating between atrophic cirrhosis, on the one hand, and chronic passive congestion or pseudo-cirrhosis, on the other. Bauer,<sup>28</sup> however, states that it occurs in almost all diseases of the liver.

It is purely a qualitative test for the existence of liver disease. It probably has the advantage of specificity, since to no other cells has been ascribed the ability to convert urobilinogen into the ordinary bile pigments. From their own work and from a study of the literature, Falk and Saxl<sup>29</sup> conclude that urobilin excretion occurs in very slight injury to the liver, in which it is impossible to detect decreased carbohydrate tolerance or the N partition changes characteristic of insufficiency.

#### FIBRINOGEN.

Doyon and Kareff,<sup>30</sup> and Nolf<sup>31</sup> and his school showed that the extirpation of the liver was followed by the rapid disappearance of fibrinogen from the blood. In the report of an occasional experiment on animals, Doyon and his co-workers,<sup>32, 33</sup> showed that decreased fibrinogen content occurred after chloroform poisoning, and Corin and Ansiaux<sup>34</sup> and Jacoby that it occurred also after phosphorus poisoning.

According to Whipple and Hurwitz,<sup>35</sup> fibrinogen normally exists in plasma of dogs in amounts varying between 0.2 to 0.5 gm. per 100 cc. blood. With the occurrence of liver injury produced by chloroform poisoning it decreases, falling at the time of injury and returning to above normal during the repair which rapidly follows. It may be present in such small amounts that hæmorrhage or hæmorrhagic tendency results, the clots being too soft to check bleeding.

In cases of acute hepatic disease (chloroform poisoning) in dogs and human beings it may fall to 0.048 to 0.034 gm. per 100 cc. blood, in chronic liver cirrhosis (Whipple<sup>36</sup>) to 0.05 gm. or even lower. This decrease is not constant. A high fibrinogen content may exist in the presence of definite liver disease. However, when the content is low it is of grave prognostic import.

The test is made as follows: 25 or 50 cc. of clear plasma obtained by centrifugalizing the blood, which has been received into oxalate solution, is heated in a water bath at

\* Excellent reviews of this whole subject are given by v. Frey<sup>10</sup> and by Falk and Saxl.<sup>29</sup>



59° C. for 20 to 30 minutes. Fibrinogen is thrown out as a white flocculent precipitate, is collected on a Gooch crucible, washed with  $H_2O$ , alcohol and ether, dried and weighed.

#### LIPASE.

The amount of lipase in the blood has been shown to be markedly increased in certain diseases of the liver (Whipple, Mason & Peightal).<sup>44</sup> They utilized Loevenhart's<sup>45</sup> method of determining lipase, which is done according to the following technic: Four tubes are prepared, each containing 1 cc. of plasma, or serum, diluted with 4 cc. of distilled  $H_2O$  and to this is added 0.3 cc. toluol to prevent bacterial infection. To two of the tubes is added 0.26 cc. of ethyl butyrate, the other two serving as controls. After shaking, the tubes are stoppered and placed in an incubator at 38° C. for 18 to 24 hours, then cooled in water and to each is added three drops of azolitmin as an indicator. They are then titrated in pairs to neutrality, the controls with 1/10 N acid, the other with 1/10 N alkali. The controls with this indicator show the blood alkalinity to be 0.1 cc. of N/10 acid, while the butyrate tubes show an acidity of 0.1 to 1.2 cc. of N/10 alkali. The lipolytic activity of normal blood or serum expressed in terms of N/10 HCl is, therefore, 0.2 to 0.3 cc. .

Experimental injury to the liver resulting from chloroform, phosphorus, hydrazine, etc., always produces an increase in plasma lipase to from 2 to 8 times the normal. After chloroform anaesthesia of 1 to 2 hours' duration, in dogs the plasma lipase increases to 1 to 2 cc. N/10 acid. This increase occurs during the first few hours after anaesthesia, lasts two to three days, and then slowly decreases as repair is established, finally reaching normal again on complete recovery. If the animal be fatally poisoned, the lipase remains high until death on the fourth or fifth day.

The test has been applied clinically by Whipple in a limited number of cases. A case of eclampsia showed a very high plasma lipolytic activity and at death showed hæmorrhagic portal liver necrosis. Pneumonia, peritonitis, leukaemia, and various infections show an increased lipase, at times more than double the normal. Early stages of liver cirrhosis show a high lipase while late stages may, unless complicated with some liver necrosis, show a low lipase. A normal content was found in pernicious vomiting, uræmia with convulsions, in jaundice and obstructive jaundice of months' duration.

#### GHEDINI'S FERMENT TEST.

Within the current year Ghedini<sup>46</sup> has proposed a new test which is based upon the presence in the blood serum of a ferment which he claims arises in the liver cells and which is capable of converting glycogen into maltose, isomaltose, and glucose. In short, this must be a test for two blood ferments, diastase and maltase. Diastase varies tremendously in normal sera, consequently, *a priori*, this in itself would vitiate the test. Sufficient evidence has not been presented to establish the liver as the sole source of the ferment or ferments involved.

#### GENERAL CRITICISM OF FUNCTIONAL TESTS.

With the exception of the urobilinogen test, none of these deal with functions which can be said with certainty to be specific of the liver, since the muscles play a large rôle in carbohydrate metabolism, and the kidney, according to recent work of Van Slyke,<sup>47</sup> possibly participates in the conversion of amino acids into urea. The results of the tests seem to be inconstant, with the possible exception of the urobilinogen test, which is positive in most mild diseases of the liver. However, it only indicates the existence of liver injury and gives no conception of its extent.

Technical difficulties are encountered in some of the tests. The administration of large amounts of carbohydrates leads to nausea, vomiting, and diarrhoea, all of which vitiate the test. Considerable chemical training and equipment are necessary to carry on the work in relation to the nitrogenous metabolism, while large quantities of blood (50 cc.) are necessary for the fibrinogen studies.

Since the tests most used clinically have lacked a quantitative side they have proven of much less value from the standpoint of prognosis than similar studies in relation to the kidney. They have indicated only the presence of disease, but not the extent of involvement. Furthermore, the lack of clinical and autopsy data in the various publications detracts from their value, since one cannot form conclusions concerning the value of the findings in the individual cases.

#### PHENOL-TETRACHLOR-PHTHALEIN.



This compound was first prepared by Orndoff<sup>48</sup> and Black,<sup>49</sup> of Cornell University, in 1908. Its pharmacological properties were studied by Abel and Rowntree<sup>50</sup> in 1909. "Its physical and chemical properties present such similarities to those of phenolphthalein that one is surprised to learn that there are certain well-marked pharmacological differences between them. Like phenolphthalein, it is an odorless, tasteless, crystalline compound, insoluble in water and forming deeply colored hydrolizable salts with alkalis. Its ionization constant has not yet been determined, but its avidity as an acid cannot be far removed from that of phenolphthalein, inasmuch as solutions of its salts (Na or K) are promptly decolorized on the addition of serums or by contact with animal tissues. In this respect its salts differ in no way from those of phenolphthalein. The two compounds have, on the whole, a very similar pharmacological action."

\* It is with great pleasure that we take this opportunity of expressing our gratitude to Professor Orndoff for his kind response to our repeated requests for the phenol-tetrachlor-phthalein used in this and other studies.

From the pharmacological studies of Abel and Rowntree<sup>40</sup> it was learned that phenol-tetrachlor-phthalein itself was non-irritant locally, but that solutions of its alkali salts administered subcutaneously act as decided irritants unless they are highly diluted since "such salts formed as they are by neutralizing a very weak acid with a very strong base are strongly hydrolyzed in aqueous solution and hence act upon the tissues like solutions of caustic soda." It was further learned in animal experimentation that the tetrachlor body has a very low toxicity; that it exercises no hemolytic influence; that it does not affect the coagulability of the blood; that, associated with its rapid intravenous injection, there occurs a fleeting drop of blood pressure which is followed by a slight increase (15 to 25 mm. Hg.) lasting 10 to 20 minutes, provided large injections are given; that it possesses no bactericidal or antiseptic properties; that it does not influence the rate of flow of either pancreatic juice or bile; that it appears in the bile first as a conjugated body and later in its free form, that in moderate quantities, following its subcutaneous administration in olive oil or its intravenous injection as a disodium salt, it escapes from the body only in the bile, the amount that passes into the intestines in other secretions being so minute that it can barely be detected; that a small amount is re-absorbed from the large intestine and that administered in a dose of 0.4 gm. in olive oil subcutaneously it exhibits laxative properties.

Further work showed that clinically the drug administered in olive oil displayed definite laxative characteristics, but that its low solubility in oil, necessitating a large bulky injection, stood in the way of its general adoption in this connection.

The effect of slight changes in the chemical formula of some of these phthaleins upon their pharmacological behavior, especially as to the channel of their excretion, is exceedingly interesting. Phenolphthalein given in moderate quantities subcutaneously in oil or intravenously as the disodium salt is excreted both in the urine and in the bile. The replacement of the CO by an SO<sub>2</sub> group yields phenolsulphonophthalein for which the kidney is the chief organ of excretion, while the substitution of the hydrogen atoms of the phthalein radical of phenolphthalein by four chlorine atoms gives phenol-tetrachlor-phthalein, the excretion of which is specific to the liver.



The specificity displayed by the kidney in the secretion of phenolsulphonophthalein together with its tinctoral properties which are ideally adapted for quantitative work, led to the introduction of this body as a renal functional test in which

connection it has proven of the greatest value prognostically and diagnostically, and from the standpoint of treatment.

The striking specificity displayed by the liver towards the excretion of this dye suggested to one of us (R.) the possibility of utilizing the drug as a functional liver test, the underlying principle involved being identically that concerned in the phenolsulphonophthalein test of kidney function, *e. g.*, the specific excretion of a dye by a single organ and the decreased capacity for its excretion consequent upon lowered function resulting from disease.

With this idea in view the normal quantitative excretion was investigated and determined in rabbits to be from 30 to 45 per cent of the amount injected. The possibility of utilizing tetrachlorphthalein as a test for liver function was suggested to Dr. G. H. Whipple, who very kindly applied the test to a series of dogs suffering from experimental liver lesions. These preliminary tests showed a marked decreased excretion to exist in disease. A simultaneous clinical and experimental study has been carried on, the results of the experimental work being reported in this number of the BULLETIN by Whipple, Peightal and Clark.

#### METHOD OF PREPARING SOLUTION FOR INJECTION.

The preparation injected is an aqueous solution of the disodium salt prepared as follows:

2.5 gm. of phenol-tetrachlor-phthalein are placed in a 200 cc. Erlenmeyer flask with 5 cc. of 2/N NaOH solution and 45 cc. of freshly distilled water. This is boiled for 20 minutes under a reflux condenser. The solution is filtered into a 100 cc. flask, when it is ready for use. This gives approximately a 5 per cent solution which is almost isotonic with the blood.

The solution is an intense purplish red color. It will not keep for more than a few days since the phthalein is precipitated by CO<sub>2</sub> from the air. Even when CO<sub>2</sub> is excluded some precipitation still occurs from the loss of the alkali through union with the silicates of the glass container. In the event of only a small amount of precipitate, sterile filtration can be carried out and the resulting solution used for injection, provided a fresh standard for comparison is prepared.

#### METHOD OF ADMINISTRATION.

Arbitrarily 8 cc. of this solution, approximately 400 mg. of tetrachlor-phthalein has been selected. This amount is sufficient to give a most intense purplish red color to 20 litres of water. Its administration in health is never followed by the appearance of the dye in the urine,\* and this amount insures in health an intense color in the final preparation of the faeces which is used for the quantitative determination.

The dye is administered intravenously by gravity with antiseptic and aseptic precautions and with the usual intravenous technic. The funnel and system are filled with freshly

\* In health the dye has been recovered in the urine of a normal patient following injection of 0.5 gm.

distilled water and after the flow is well established the phthalein solution is added. Fifty to 100 cc. of water are used and the phthalein solution is washed in with freshly distilled water until the fluid entering the vein is colorless. Ten to 15 minutes are required for its administration. Physiological salt solution may be preferable to distilled water for use in this injection.

#### COLLECTION OF MATERIALS FOR STUDY.

Active purgation is instituted prior to administration of the dye and throughout the time of observation, usually by means of compound cathartic pills. The stools are collected for 48 hours, the urine for 24 hours. In the event of little or no feces being obtained enemata are used, but unless the normal amount of dye is recovered, the test must be discarded, since low findings under these conditions could not be accepted.

#### METHOD OF DETERMINING THE AMOUNT OF PHTHALEIN IN STOOLS.

The total 48 hours feces are placed in a 2 L. bottle and diluted with water to 1 or 1.5 L. depending on their amount. This is placed in a shaking machine for from 5 to 20 minutes. Without allowing time for sedimentation 1/10 of the total is placed in a 1 L. flask and to this is added 5 cc. of 40 per cent NaOH which causes the mixture to take on a dirty red color. Dilution is made with water to 1 L. A stopper is inserted and the mixture thoroughly shaken. One hundred cubic centimeters of this preparation is placed in a 200 cc. flask, 5 cc. of saturated basic lead acetate added, resulting in a decolorization of the mixture and the throwing out of a heavy lead precipitate which carries down all of the pigments, leaving a clear colorless supernatant fluid. Five cubic centimeters of 40 per cent NaOH are added; this again elicits the red phthalein color, but does not redissolve the other lead pigment combinations. In certain instances 5 cc. of NaOH at this point are not sufficient to elicit the maximum intensity of red and more should be added until the maximum is reached, but not sufficient to free the other pigments from their insoluble lead combination. The contents of the flask are made up to 200 cc., shaken, and a small part filtered off, or the solution is allowed to stand five minutes, when in many cases a clear red supernatant fluid ready for estimation can be decanted off. This solution is compared in the Rowntree and Geraghty modification of the Autenrieth Königsberger colorimeter with a 20 mg. to a litre solution of disodium salt of tetrachlor-phthalein (*e. g.*, 0.4 cc. of the original solution to 1 L. plus sufficient NaOH to insure maximum color). With these dilutions the amount of dye present is indicated directly in per cent.

When the amount recovered is below normal, it is advisable to add 2 to 3 cc. more alkali to the 200 cc. preparation and redetermine, thus insuring that the maximum color has been elicited. The addition of large quantities of alkalies is undesirable, since it sets free the other pigments, rendering the solution yellowish red instead of purplish red.

Not more than ten minutes are required to carry out the test after the feces are removed from the shaker.

Where difficulty is experienced on account of the quality of the color, the following procedure, which may prove of some value in certain instances, may be utilized. After the addition of about 10 cc. of 40 per cent sodium hydroxide, the feces are made up with water to one litre. To 1/10 of this is added 5 cc. of sodium hydroxide and water up to one litre. Of this 100 cc. is placed in a 200 cc. flask and to it 5 to 10 cc. or more, of a calcium chloride mixture\* is added until the best quality of color is elicited. Dilution is made to 200 cc., the mixture is allowed to stand from one-half to 24 hours, a small amount of the supernatant fluid is filtered off, and read against the standard.

In our earlier methods an attempt was made simply to dilute the feces, filter off and determine the amount present, but quantitative determination is usually impossible in this way on account of the large amount of coloring matter present in the mixture. Later basic lead acetate was used and the precipitate collected on a filter, extracted repeatedly with hot alkaline alcohol and the alcohol diluted to the proper extent, alkali added and determinations made. This method was time consuming, required much alcohol, and the extraction of tetrachlor-phthalein was never complete. Finally the method presented above was devised.

#### ACCURACY OF METHOD.

A number of procedures were utilized to determine the degree of accuracy of the method and to determine what part the personal equation plays in regard to it.

Is the total dye substance recovered? Accurately measured amounts of the original solution of the disodium salt were added to the feces, thoroughly mixed by one member of our group, and determined by another who was unfamiliar with the amount added. In certain instances independent readings were made by the entire group. The results are as follows:

TABLE I.

Number	Amount added	Amount recovered		
		B	R	H
I	25 %	.....	23.5%	.....
II	12.5%	.....	12 %	.....
III	12.5%	12 %	12.5%	12.5%
IV	9.4%	8 %	10 %	10 %
V	25 %	23.5%	23 %	22.5%
VI	18.8%	17 %	19 %	17 %

Since only an aliquot portion of the feces is used for the determination, the necessity of justifying this procedure seemed advisable. This was done as follows: The technic was performed on several fractions by one and readings made on the final solution by the three members of the group. The results in per cent are shown in Table II.

\* CaCl<sub>2</sub> 90 gm.  
Conc. NH<sub>4</sub>OH 10 cc.  
Water 50 cc.



TABLE II.

Number.	R	B	H
I	16 %	14 %	16 %
II	16 %	15 %	17 %
III	17.5%	15.5%	16 %
IV	16 %	14 %	15.5%
V	17 %	14.5%	17 %
VI	16.5%	15 %	17 %
VII	16 %	13.5%	15 %

From the table it will be seen that differences in reading the same solution may occur where various individuals are making the readings, R. reading constantly lower than B. or H., the difference, however, never being greater than 2.5 per cent.

Simultaneously it is seen that slight differences occur in different fractions, as evidenced by III and VII, the latter being lower according to all three observers. Here again, however, the difference is only slight.

It was also considered advisable to check the readings on various fractions at the point where lead acetate is added. The following table shows a series of readings of different fractions:

TABLE III.

Number.	R	B	H
I	29 %	30 %	29 %
II	28.5%	30 %	28 %
III	29 %	29.5%	28.5%
IV	28.5%	29.5%	28 %
V	28 %	29.5%	27 %
VI	28.5%	29 %	30 %
VII	29.5%	29.5%	29.5%

No destruction of the dye occurs after the stools are collected, so that immediate determination is not necessary. The following table indicates the stability of the drug.

TABLE IV.

Patient	Time of determination	Time of exposure	Stability of color
P.	54%	1 week	55 %
M.	18%	1 "	20 %
L.	47%	5 "	45 %
McC.	31%	5 "	33 %
S.	28%	7 "	32 %
G.	33%	12 "	33 %
B.	26%	15 "	24.5%
A.	26%	19 "	23 %

No preservatives were used so that decomposition of the dye does not apparently result from bacterial infection. Slight differences in the readings can be explained possibly by differences in the standards used for comparison, since in the first instance each test was made from the standard prepared from the solution injected, whereas all of the later readings were made against a single freshly prepared solution.

It is evident, therefore, that the test, though not absolutely quantitative, gives reliable results approximately correct, and that dependence can ordinarily be placed upon its findings, errors of more than 5 per cent being rarely encountered. Difficulties may arise at times, as will be seen later.

### UNDESIRABLE FEATURES OF THE TEST.

The collection of total faeces for 48 hours is the most difficult part of the technic to control. It certainly constitutes an objectionable feature of the test. Simple as it may seem, even in the best institutions, except under special provisions, it is difficult to find a corps of attendants capable of carrying out proper collections. Despite all precautions, in four instances some of the faeces was lost in collecting. In these cases no drug at all, or a small amount only (at most 10 per cent), was recovered, the patients showing neither signs nor symptoms of liver involvement. Repetitions within a week in each instance revealed a normal, or practically normal excretion. Careful questioning of patients and attendants showed in one or two instances that losses undoubtedly had occurred.

In two other cases, both myocardial decompensation, repetition of the test within a week showed a tremendous increase in the dye output. Hesitation is felt in claiming that the increase was entirely due to improvement in liver function, although both cases were in *extremis* at the time of the first test and clinically in fair condition at the time of repetition. Until other such cases are encountered where more certainty exists in relation to total collection, losses in collection cannot be excluded as the cause of the low output in the first instance.

The collection over 48 hours has a second objectionable feature. The excretion of the drug occupies but 12 to 18 hours in health, consequently 48-hour collections are apt not to show minor grades of injury so well, since the continuous secretion of smaller amounts of the dye over longer periods, 24 to 36 to 48 hours, may bring the total output close to normal.

The quality of red color obtained in certain instances constitutes the third objectionable feature of the test. This objection is minimized by the method now utilized. However, with the best technic the color finally obtained may in a considerable proportion of cases (10-20 per cent) exhibit yellowish red or brownish red qualities instead of the purple red desired. Such determinations are less accurate, but only in rare instances does the color constitute a very serious difficulty.

In myocardial insufficiency with feeble circulation localized thrombosis of the veins at the point of injection may occur. This has been encountered in ten instances in this series. Slight local pain together with resistance offered to the palpating finger was noted. Thrombosis, however, was not encountered except in myocardial insufficiency, marked anæmia, or where advanced phlebosclerosis was present. The introduction of large quantities of fluids is inadvisable in the presence of a weak myocardium and consequently in this connection great dilution cannot be utilized.

The fate of the unrecovered portion is unknown. Apparently, however, no destruction of the drug occurs after its entrance into the intestinal tract, since the amount of drug recovered in a dog's faeces corresponds closely to that recovered directly from a permanent biliary fistula following the same dosage.

The test is inapplicable where obstruction to the biliary passages exists and is, therefore, limited in its application.

TABLE V. NORMAL CONTROLS.

No.	Name.	No.	Diagnosis.	Age— yrs.	Date— 1913.	Per cent. in urine	Remarks.
1.	S. H.		Normal.	27	1-28	30	
2.	A. B.		Normal.	25	1-28	30	
3.	B. E.	87296	Convalescent typhoid.	22	2-15	42	Temperature normal for 1 week.
4.	C. McC.	87584	Splanchnoptosis	32	2-22	39	
5.	F. B.	87617	Orthostatic albuminuria.	17	2-22	31	
6.	A. L.	87810	Neurasthenia	45	2-28	52	
7.	A. A.	87907	Diabetes.	48	3-5	40	
8.	M. M. C.	87809	*Chronic tuberculosis.	44	3-10	22-33	Afebrile 1 week; earlier 22%.
9.	J. M.	88157	Neurasthenia	60	3-10	52	
10.	D. W.		Convalescent pneumonia.	27	6-10	24	Afebrile 1 week.
11.	L.		Convalescent malaria.	22	6-10	48	Afebrile 6 days.
12.	L. F.	89350	Rheumatic fever convalescent	24	5-29	30	Afebrile 1 week.
13.	C.		Pulmonary tuberculosis.		6-13	39	Afebrile.
14.	W.		Fracture of femur.		6-17	42	
15.	K.		Fracture of femur.		6-17	34	
16.	A.		Gunshot wound.		6-20	40	( <sup>1</sup> )
17.	B.		Fracture.		6-20	35	( <sup>1</sup> ) 500 mg. injected.
18.	M.		Gonorrheal arthritis.		6-20	34	

(<sup>1</sup>) + Slight. (<sup>2</sup>) + Considerable.

TABLE VI. FEBRILE CASES.

No.	Name.	No.	Diagnosis.	Age— yrs.	Date— 1913.	Per cent. in stool.	Urine.	Remarks.
19.	G. S.	87326	Pulmonary tuberculosis; pleurisy with effusion.	43	2-7	43		99-102° F.
20.	J. F.	86802	Pulmonary tuberculosis; pleurisy with effusion.	34	2-7	40		99-102° F. for 2½ months.
21.	I. B.	87671	Typhoid fever.	14	2-28	27		15th day of fever.
22.	S. T.	88038	Acute lobar pneumonia.	18	3-10	39		Fifth day of disease temperature 104-105° F.
23.	A. B.	87794	Acute tubercular pleurisy with effusion.	28	3-19	43		Continuous fever 104° F. for over 1 month.
24.	B. K.		Acute rheumatic endocarditis.	30	3-19	40		Temperature 103° F. for 1 month.

TABLE VII. ANAEMIA.

No.	Name.	No.	Diagnosis.	Age— yrs.	Date— 1913.	Per cent. in stool.	Urine	Hb.	R. B. C.
25.	C. R.	88350	Hypernephroma	56	3-29	41		28	1,600,000
26.	O. K.	88692	Secondary anaemia; hemorrhoid.	21	4-24	35		21	2,680,000
27.	J. S.	88675	Pernicious anaemia.	20	4-23	18-20		31	1,700,000
28.	W. S.	88825	Secondary anaemia.	45	4-27	28		23	2,700,000
29.	H.		Gastric carcinoma.	38	5-24 6-10	14 24		20	2,300,000
30.	L. F.		Gastric carcinoma.	39	6-10	20		22	2,800,000

The possibility of utilizing the time required for the disappearance of the drug from the blood after its administration is being tried in the hope that some of these difficulties may be surmounted.

#### THE RESULTS OF THE TEST.

Eighty determinations of liver function have been made in 67 patients. The series contains normal controls and various types of liver injury.\* The test was applied in 24 cases in which the livers were believed to be normal. The amount of drug excreted varied from 30 to 52 per cent, as will be seen in Tables V and VI. In one constipated patient only 24 per cent was recovered.

Cases in Table VI are considered as normal controls, since the excretion is normal with one exception, a case of typhoid (third week) in which focal necrosis cannot be excluded. The average output in afebrile normal cases was 37.4 per cent, while that in the febrile class was 39 per cent. The lower limit of normal is, therefore, considered 30 per cent for 48 hours.†

Dogs with biliary fistulae furnished some interesting data in relation to the rate of normal excretion of the drug. It appears in the bile in its free form regularly within 10 to 15 minutes following the intravenous administration of 100 to 200 mg. The same time is required in human beings, since, in the one case studied after operation, the drug was present in the bile after 15 minutes. The largest amount recovered from dogs was 55 per cent. The maximum excretion is quickly reached, since in one instance 27 per cent was recovered during the first 6 hours. In health excretion is complete within 16 to 20 hours.

The dye output is independent of the quantity of the bile excreted. Following the injection of the same amount of phthalein into the same dog more dye was recovered in 8 cc. in one instance than in 80 cc. of bile in another instance. This is analogous to the independence between the amount of sulphonephthalein excreted and the quantity of urine.

#### INFLUENCE OF FEVER.

Pyrexia *per se* has no effect upon liver function, as will be seen from Table VI. Case Q. T. was an acute febrile condition with temperature 104° to 105° F. at the time of the test, and case A. B., a chronic one, the temperature reaching 104° F. every day for over a month, yet both showed a normal phthalein output. Case I. B. is discussed above.

#### INFLUENCE OF ANEMIA.

In severe grades of secondary anemia a normal, or practically normal, output may be encountered, as in cases O. K. and W. S., Table VII. From these cases it is justifiable to

conclude that secondary anemias of slow development must be of an extreme grade before liver function is affected. Experimental evidence indicates, however, that acutely developing severe secondary anemia does influence the phthalein output, as will be seen from the following protocol.

#### Female Dog. 18.5 Kg.

- 5-3-13. Excreted 35 per cent tetrachlorphthalein.
- 5-9-13. Bled 640 cc. The following morning Hb. 64 per cent. R. B. C., 4,800,000. Injected 200 mg. phthalein.
- 5-12-13. Hb. 75 per cent. Phthalein recovered 41 per cent.
- 5-13-13. Bled 600 cc.—ether anaesthesia. The following morning Hb. 48 per cent. R. B. C., 3,840,000. Phthalein injected.
- 5-16-13. Hb. 50 per cent. Phthalein recovered 30 per cent.
- 5-18-13. Bled 650 cc.—ether anaesthesia. The following morning Hb. 42 per cent.
- 5-20-13. Hb. 42 per cent. Phthalein recovered 15 per cent.\*
- 5-26-13. Bled 600 cc. The following morning Hb. 30 per cent. R. B. C., 2,400,000.
- 5-29-13. Phthalein recovered 13 per cent.
- 6-12-13. Phthalein recovered 27 per cent.
- 7-7-13. Hb. 90 per cent. R. B. C., 5,586,000. Phthalein injected.
- 7-9-13. Phthalein recovered 39 per cent.

A second dog responded in the same way, the phthalein decreasing from 50 per cent to 10 per cent, at which time the Hb. was 30 per cent and the R. B. C. below 2,000,000. This dog, however, had been accidentally inoculated with sarcoma which was unexpectedly discovered from microscopical study of the liver, the dog dying on the table during the last bleeding.

There exists a striking analogy in the influence of secondary anemia on liver and on kidney function, as will be seen by comparing the above protocols with experiments previously reported by Rowntree and Geraghty<sup>51</sup> on the influence of anemia on kidney function.

The two cases of anemia secondary to gastric carcinoma show decreased function. However, metastasis cannot be excluded in either instance. In severe phenyl hydrazine anemia in dogs Whipple saw but little influence on liver function. In the single case of pernicious anemia a decreased output was found.

From such a limited number of cases no conclusions can be drawn except that secondary anemia must be of an extreme grade before the excretion of the dye is decreased. The experimental results suggest the necessity of more observation along these lines.

#### HEPATOPATHIES.

Thirty-seven cases exhibiting signs or symptoms of abnormalities of the liver have been investigated, the series including enlargement dependent upon cardiac disease, cirrhosis, carcinoma, amœbic abscess, luetic hepatitis, cholecystitis, and enlargement associated with leukemia. A detailed description of the history and clinical findings of each of these cases, together with the phthalein output, is appended. Table VIII shows the results of the test in these cases.

\* 57 per cent of sulphonephthalein was recovered in two hours. This indicates only a slight reduction in kidney function.

\* We wish to express our thanks to Dr. Ernst Zueblin of the University of Maryland Hospital, to Drs. Boggs and Snowden of Bay View Hospital, and to the Medical and Surgical staffs of our hospital for the opportunity of studying the clinical material.

† 48-hour collections are necessary, since in several instances an appreciable amount of dye (8 to 10%) was recovered in the second 24 hours.



TABLE VIII. PATHOLOGICAL LIVERS. HEPATOPATHIES.

No.	Name.	No.	Clinical diagnosis.	Age yrs.	Date 1913.	Per cent. in stool.	Urine.	Remarks.
31.	C. H. ....	87440	Myocardial insufficiency; acute endocarditis; tuberculous polyserositis.	47	1-7 2-14 4-26	7 18 15	..	Autopsy.
32.	T. A. ....	87515	Arteriosclerosis; chronic nephritis; mild myocardial insufficiency.	39	2-5	28	..	
33.	R. S. ....	87589	Myocardial insufficiency; arteriosclerosis.	36	2-15	9	..	
34.	M. L. ....	87653	Myocardial insufficiency; mitral insufficiency and stenosis; adherent pericardium.	48	2-22	33	..	
35.	P. G. ....	87770	Myocardial insufficiency; aortic and mitral insufficiency.	23	2-28	42	..	
36.	C. G. ....	87747	Myocardial insufficiency; chronic bronchitis; emphysema; cirrhosis of liver?	66	2-28	33	..	
37.	R. B. ....	87855	Myocardial insufficiency; arteriosclerosis.	45	3-5	8	..	Small specimen of stool.
38.	C. G. ....	88093	Myocardial insufficiency; myocarditis; acute endocarditis.	51	3-15	35	..	Autopsy.
39.	J. F. ....	88071	Myocardial insufficiency; mitral stenosis and insufficiency.	40	3-15	33	..	
40.	B. S. ....	88324	Myocardial insufficiency; mitral insufficiency and stenosis; aortic insufficiency.	27	3-24	33	..	Died 4-12. No autopsy.
41.	E. G. ....	88884	Myocardial insufficiency; dilated aortic arch; syphilis; chronic nephritis?	42	4-27	32	..	
42.	J. J. ....		Myocardial insufficiency; aortic insufficiency; dilated aortic arch; syphilis.	43	5-12 5-19	5* 24	..	Autopsy 6-15-13.
43.	T. G. ....	89247	Arteriosclerosis; myocardial degeneration; chronic nephritis	52	5-17 5-24	30 28-30	..	
44.	I. W. ....	89144	Myocardial insufficiency; arteriosclerosis.	48	5-22	28	..	
45.	I. B. ....	89301	Miliary tuberculosis; tuberculous pericarditis (adherent); myocardial insufficiency.	26	5-27	21	..	Autopsy.
46.	S. R. ....	89417	Myocardial insufficiency.	33	5-24 6-3	7 33	..	In severe cardiac break. In good clinical condition.
47.	R. P. ....	( <sup>1</sup> )	Myocardial insufficiency.	..	4-28	35	..	
48.	M. ....		Myocardial insufficiency.	40	6-13	20	..	In moderate cardiac decompensation.
49.	J. N. ....	88072	Cirrhosis of liver.	52	3-10	23	..	Normal fibrinogen; clinically well, admitted only for test.
50.	D. M. ....	( <sup>2</sup> )	Cirrhosis of liver.	56	3-26	6	..	Special precautions in collecting specimens.
51.	W. G. ....	( <sup>1</sup> )	Myocardial insufficiency; cirrhosis of liver.	..	4-28	43	..	Died about 3 weeks later. No autopsy.
52.	K. Fischer. ....	( <sup>3</sup> )	Carcinoma of stomach; metastasis to liver.	48	3-19	8	1.5%	Autopsy.
53.	A. Hepburn. ....	( <sup>2</sup> )	Carcinoma of gall bladder.	67	4-22	20	..	
54.	E. S. ....	88424	Carcinoma of stomach with metastasis.	33	3-31 4-8	6* 24	..	Unsatisfactory specimen of stools.
55.	G. D. ....		Carcinoma of stomach with metastasis to liver.	72	..	14	..	
56.	M. S. ....	87656	General abdominal carcinomatosis.	40	3-5	39	..	
57.	J. T. ....	89781	Carcinoma of liver.	45	6-20	7	( <sup>1</sup> )	Collection for 30 hours.
58.	M. B. ....	87983	Suspected amoebic abscess of liver.	27	3-10	33	..	Explored; no abscess found.
59.	J. T. ....	( <sup>1</sup> )	Amoebic abscess of liver; drained.	45?	4-28	23	..	
60.	F. R. ....	88825	Hepatitis; tuberculous peritonitis (?)	40	4-27	30	..	Unimproved on discharge.
61.	E. P. ....	88861	Splenomegaly; perihepatitis (?)	19	5-10	23	..	Discharged; condition unchanged.
62.	J. McC. ....	89082	Tuberculous peritonitis (?); syphilitic hepatitis (?); mitral insufficiency.	52	5-17 6-10	31 32	..	
63.	J. K. ....	89439	Acute cholecystitis.	56	5-29	28-30	..	Discharged; well.
64.	H. A. ....	89593	Tuberculous peritonitis (?); liver cirrhosis (?)	52	6-7	22	..	Discharged; condition unchanged.
65.	E. T. ....	( <sup>2</sup> )	Syphilis of liver; syphilitic endocarditis; mitral insufficiency.	33	4-22	18-22	..	
66.	G. S. ....	( <sup>2</sup> )	Syphilitic hepatitis (?); amyloid liver (?); pulmonary tuberculosis.	27	4-22	40	..	Autopsy.
67.	R. S. P. ....		Lymphatic leukaemia.	..	6-13	55	..	

## MYOCARDIAL INSUFFICIENCY.

Eighteen of the hepatopathies were associated with some degree of myocardial insufficiency. In nine the phthalein output was normal. Five cases showed marked involvement of function as indicated by the test and in each instance the low output was associated with an extreme grade of broken compensation, whereas the break in the nine cases already mentioned was much less severe. In two instances a subsequent test a week later, at which time the cardiac condition was improved, revealed a marked increase in the phthalein excretion, although hesitation is felt, as intimated above, in ascribing this difference between the two findings entirely to restoration of cardiac compensation.

Of the other four cases, one with a 21 per cent output (I. B.) had miliary tuberculosis which affected the liver, one (M) in moderate decompensation excreted 20 per cent, while two others (T. A. and I. W.) were practically normal (28 per cent).

It is therefore evident that liver function as indicated by the test only becomes seriously affected in those cases in which the myocardial insufficiency is extreme. This is in striking analogy to the condition of renal function as indicated by sulphonephthalein,<sup>22</sup> for only in the cases of extreme cardiac decompensation or passive congestion, clinical or experimental, is the output of phthalein appreciably decreased. The first evidence of cardiac improvement is also associated with a prompt return of renal function to normal.

## CIRRHOSIS OF THE LIVER.

Two cases, typical clinically in every respect, have been studied. One, D. M., was *in extremis* at the time of the test, showing both toxic and obstructive symptoms. His output was only 6 per cent and no dye appeared in his urine. Death occurred two months later, but no autopsy was obtained. The other case, J. N., had been under observation for years. Six years earlier, he had 272 litres of ascitic fluid removed. For some years, however, he has been practically free of symptoms, carrying on his usual work. The patient considers himself well and exhibits but few residues of his former disease. The output, 23 per cent, is well in keeping with his present clinical condition.

Cirrhosis possibly existed in two other cases, W. G. and H. A. The former clinically looked like cirrhosis, but myocardial insufficiency was also present. A normal output was found. The patient died three weeks later, no autopsy being obtained. The existence of cirrhosis in the other patient, H. A., with a 22 per cent output, is very questionable.

The limited number of cases and the absence of autopsy data allow of no conclusions concerning the excretion of the drug in cirrhosis.

## CARCINOMA OF THE LIVER.

Three verified cases of liver carcinoma showed a decreased function. In one, K. F., the output was only 6 per cent. This patient came to autopsy, the destruction of liver tissue

being very marked, together with a uniform central necrosis involving about two-fifths of each lobule. The other patients showed 7 and 14 per cent excretion respectively, the liver involvement being marked on exploration. H., with cancer of the gall bladder, excreted 20 per cent. This patient is still living.

In one patient, E. S., suffering from carcinoma of the stomach, 24 per cent was recovered. No metastases were visible on exploration.

In one case of general abdominal carcinomatosis without liver involvement, M. S., there was no decrease in phthalein output.

## AMOEBC ABSCESS.

A week after the institution of drainage in a case of amoebic abscess of the liver (W. G.) the test was applied and 23 per cent recovered, the patient at this time being in a good clinical condition. A second suspected case showed a normal function. This case was explored by Professor Halsted and no abscess was found.

## MISCELLANEOUS LIVER CASES.

Three of these cases were very similar clinically, exhibiting an unexplained ascites. Luetic hepatitis and tuberculous peritonitis were suspected. Two showed a normal function, while 22 per cent was recovered in the other case in which liver cirrhosis also had been suggested as a clinical diagnosis.

One case of cholecystitis showed a normal function. E. P., with a diagnosis of splenomegaly and perihepatitis, excreted 23 per cent, while from E. T., with luetic hepatitis and myocardial insufficiency 18 to 22 per cent was recovered.

G. S., in whom an amyloid and luetic liver was diagnosed clinically, had a normal excretion. The patient later died of his pulmonary tuberculosis and at autopsy the liver change present was chronic passive congestion with some atrophy.

The highest phthalein output in this entire series was encountered in a case of lymphatic leukaemia with enlarged liver.

Unfortunately it has been possible to apply this test only to a limited number of diseased conditions. There still remain a number of diseases, for instance uræmia, eclampsia, pernicious vomiting, septicæmia, peritonitis, and the like, associated with intoxication and depression of functional activity in which the results of the phenoltetrachlorphthalein test may be of interest prognostically.

The number of cases studied is too small to permit of far-reaching conclusions. However, the constant findings in health, the decreased output in liver disease, the analogy between the effect of anæmia and myocardial insufficiency upon kidney and liver function as indicated by the sulphonephthalein and the tetrachlorphthalein tests, the results of the test in experimental liver lesions, and the established value of sulphonephthalein, based upon the same principle as the test in kidney diseases, all indicate that the excretion of tetrachlorphthalein will be useful in the estimation of the functional capacity of the liver.

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## APPENDIX.

- (25.) No. 88350. C. R., age 56, male, colored.  
Clinical diagnosis: Hypernephroma (rt. kidney). Metastases. Myocardial insufficiency. Chronic nephritis. Uremia. For eight months difficulty on urination with passage of blood. Much

strangury. On admission: Extreme emaciation, slight dyspnea. Heart enlarged with systolic blow. Liver dulness from fifth rib to 8 cm. below costal margin in right mamillary line where edge is indefinitely felt. Not tender. Below liver in right flank is felt a round tumor, probably kidney. No edema of feet. At time of test under rest in bed liver dulness had gone up to 2 cm. below costal margin. Blood examination: Hb., 28 per cent; R. B. C., 1,600,000. March 29, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 41 per cent. Death, April 4. Autopsy: 3901. Hypernephroma of kidney. Dilatation and hypertrophy of heart. Chronic passive congestion of lungs. Cloudy swelling of viscera, etc. Liver weighs 2300 gm. Liver. Microscopical section. The lobules show central congestion, pretty extensive hyaline necrosis, probably not over 48 hours old. The lobulation is regular.

- (31.) No. 87440. C. H., age 49, male, colored.

Clinical diagnosis: Tuberculous polyserositis. Acute endocarditis. Weakness, loss of weight, shortness of breath, gradual swelling of legs and abdomen. On admission presented signs of a myocardial break. Liver, hard, firm, smooth, to umbilicus. R. B. C., 3,000,000; Hb., 35 per cent. At time of second test conditions practically those shown at autopsy. Progressive emaciation, asthenia, anemia, persistent ascites. February 14, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 18 per cent. April 26, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 15 per cent. Autopsy: 3915. Tuberculous peritonitis, cloudy swelling of viscera, fibrous myocarditis, cardiac hypertrophy and dilatation, syphilitic aortitis. Liver weighs 2150 gm. The microscopical section shows subacute diffuse hepatitis with increase in connective tissue in all parts of each lobule and considerable deformity of liver architecture. Wandering cells of every type and scattered tubercles can be found. The liver cells show atrophy and degeneration as well as distortion.

- (32.) No. 87515. T. A., age 39, male, white.

Clinical diagnosis: Arteriosclerosis, chronic nephritis. Symptoms for about one month: Palpitation, dizziness, smothering, sensations. At time of test, heart 14 cm. to left, 5 cm. to right. Systolic puff at apex. Aortic second sound loud. Liver dulness from fifth interspace to two fingers' breadths above costal margin in right mamillary line. Bases of lungs clear. Blood pressure, 200. Nothing to indicate any abnormality of liver except perhaps slight recent temporary chronic passive congestion of liver, not present at time of test. Blood examination: Hb., 90 per cent; R. B. C., 5,000,000. February 15, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 28 per cent. Discharged March 13, 1913. Improved.

- (33.) No. 87589. R. S., age 36, male, colored.

Clinical diagnosis: Myocardial insufficiency. Arteriosclerosis. Pleurisy with effusion. Two previous admissions within past six months in badly broken compensation. At time of test, orthopnea, fluid in right chest below angle of scapula. Edema of legs. Heart, 15 cm. to left, pulse rapid (110). Liver, firm, reaches about palm's breadth below costal margin. Tenderness over it. On discharge three weeks later, no dyspnea, edema or ascites, but liver still a palm's breadth down, no tenderness. Impression: Evidently permanent induration of liver from prolonged decompensation with additional acute passive congestion at time of test. Blood examination: Hb., 60 per cent; R. B. C., 4,100,000. February 15, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 9 per cent. Discharged March 9, 1913. At no time any toxic symptoms to indicate hepatic insufficiency.

- (34.) No. 87653. M. L., age 48, male, white.

Clinical diagnosis: Myocardial insufficiency, mitral insufficiency and stenosis, adherent pericardium. Acute polyarthritis 12 years ago. Bronchitis, dyspnea on exertion, palpitation, and



precordial pain for past four winters. Comes in for these symptoms. Transient hemiplegia (embolus?) five weeks ago. At time of test, heart 12.5 cm. to left and 4.5 to right. Aortic diastolic, apical systolic and presystolic murmurs. Positive Broadbent. Border of heart dullness moves 4 cm. Lung descends slightly over cardiac flatness. No ascites or edema of extremities. Râles at lung bases. Liver felt  $\frac{3}{4}$  cm. below costal margin in mamillary line but no definite edge. Impression: Perhaps slight permanent liver induration from prolonged chronic passive congestion. (No note of condition of liver on discharge.) Nothing to indicate marked chronic passive congestion of liver or fibrosis. Blood examination: Hb., 85 per cent; R. B. C., 4,400,000. February 22, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 33 per cent. Discharged March 17, 1913. Improved.

(35.) No. 87770. P. J., age 23, male, white.

Clinical diagnosis: Myocardial insufficiency. Aortic and mitral insufficiency. Right hydrothorax. Admitted eight months previous for acute polyarthritis. History of attack six years previously. Present complaints: For three days pains in legs, back, elbows, shoulders, fever and cough. At time of test, no dyspnea or cyanosis. Right hydrothorax. Left lung clear to base. Heart 14 cm. to left and 4 cm. to right. Aortic diastolic and mitral systolic murmurs. Pulse 80. Liver dullness to costal margin; edge not felt. No edema of legs. No fever. Impression: No indication of chronic passive congestion of liver at time of test or of any chronic fibrosis. Blood examination: Hb., 84 per cent; R. B. C., 4,632,000. February 28, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 42 per cent. Discharged April 3, Improved.

(36.) No. 87747. C. G., age 66, male white.

Clinical diagnosis: Chronic bronchitis, emphysema. Cirrhosis of liver (?). Admitted in December, 1910. Diagnosis, chronic myocarditis. For six years shortness of breath on exertion. Winter cough. Pains in epigastrium since 1907, occasional nausea and vomiting. Findings on previous admission: Obesity, emphysema, chronic bronchitis, cardiac arrhythmia, no cardiac enlargement, no edema. Liver dullness from sixth rib above to 7 cm. below costal margin in mamillary line. Liver hard and not tender, edge not felt. On present admission: Chronic bronchitis, emphysema, cardiac dullness perhaps a little wide. Heart regular. No edema or ascites. Liver: Dullness to just below costal margin. Surface firm and hard, edge not felt. Impression: Liver pushed down by emphysema. Possible slight induration secondary to old myocardial condition. No definite evidence for cirrhosis. Blood examination: Hb., 87 per cent; R. B. C., 4,300,000. February 28, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 33 per cent. Discharged March 3, 1913. Improved. In good condition three weeks later.

(37.) No. 87855. R. B., age 45, male, colored.

Clinical diagnosis: Myocardial insufficiency. Arteriosclerosis. Chronic nephritis. For four years dyspnea and cough. Six months before admission swelling of abdomen and legs. Nausea and vomiting two weeks. At time of test, dyspnea, edema of lungs, heart 17.5 cm. to left and 4.5 to right. No murmurs. Liver four fingers' breadth below costal margin in right mamillary line. Firm, tenderness over it. Edema of ankles. On discharge no myocardial insufficiency. Ten days before liver dullness two fingers' breadth below costal margin; edge not felt. Impression: At time of test marked recent stasis in liver. Probably some chronic induration of liver from prolonged myocardial insufficiency. Blood examination: Hb., 80 per cent; R. B. C., 5,500,000. March 15, 1913, injected 380 mg. Amount in urine, 0. Amount in stools, 8 per cent. Small specimen stool.

(38.) No. 88093. C. G., age 51, male, white.

Clinical diagnosis: Myocardial insufficiency, myocarditis, acute endocarditis, pulmonary and renal infarctions. Thrombosis of

left iliac veins. Indefinite spell of edema of feet two years ago. No symptoms until two weeks ago, when he had dyspnea, pain in side, and swelling of legs. At time of test, moderate dyspnea; no edema or ascites; liver indefinitely felt three fingers' breadth below costal margin. On admission four days before, edema of legs, dyspnea and cyanosis. Heart 16 mm. to left and six to right. Liver from fifth interspace to 7 cm. below costal margin. Edge readily felt, rounded and firm, surface smooth. Subsequently developed an active endocarditis with fever, leucocytosis, infarctions. Died April 19. Impression: At time of test acute chronic passive congestion had practically cleared up. No evidence of chronic induration. Blood examination: Hb., 91 per cent; R. B. C., 4,300,000. March 15, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 35 per cent. Death. Autopsy: 3909. Thrombosis at site of injection. Liver 1900 gm. Surface slightly roughened. Typical nutmeg liver. Dark almost black central zones and yellow opaque looking partial zones. Liver. Microscopical section shows evidence of extreme passive congestion with central atrophy and fatty degeneration. There is some increase in connective tissue about the margins of the lobule, not, however, a definite cirrhosis.

(39.) No. 88071. J. F., age 40, male, white.

Clinical diagnosis: Myocardial insufficiency. Mitral stenosis and insufficiency. Acute and chronic bronchitis. Emphysema. Two previous admissions within past year with broken compensation and large tender liver. On admission March 10, 1913, dyspnea, cyanosis, enlargement of heart 16 cm. to left and 5 cm. to right; cardiac murmurs; no edema of ankles; general bronchitis; no ascites. Liver dullness from fifth interspace to 4 cm. below costal margin where it is indefinitely felt. At time of test, only slight dyspnea, no edema or ascites, slight cough. Liver felt 3 cm. below costal margin. Edge not distinct. Impression: Slight clearing chronic passive congestion. Nothing to indicate red atrophy of liver. Blood examination: Hb., 77 per cent; R. B. C., 5,200,000. March 15, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 33 per cent. Discharged much improved.

(40.) No. 88324. B. S., age 27, male, white.

Clinical diagnosis: Myocardial insufficiency. Mitral insufficiency and stenosis. Aortic insufficiency. Pulmonary infarctions. Acute polyarthritis seven years ago. Three months ago, cough, blood-tinged expectoration, dyspnea, palpitation. Four to five weeks of swelling of legs. On admission: Enlarged heart with murmurs. Diffuse bronchitis and edema of lungs. Ascites, edema of legs. Dyspnea. Liver edge indefinite, felt 3.5 cm. below costal margin. Tender over it. Test four days later: Condition essentially same but less marked. Five days later sudden rise of temperature. W. B. C., 13,000. Jaundice. April 12, collapse, death. Impression: At time of test moderate acute passive congestion of liver. Nothing to suggest any chronic changes. Blood examination: Hb., 86 per cent; R. B. C., 5,000,000. March 29, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 33 per cent. No autopsy. Thrombosis at site of injection.

(41.) No. 88884. E. G., age 42, male, colored.

Clinical diagnosis: Myocardial insufficiency. Dilated aortic arch. Syphilis. Chronic nephritis. History of cardiac failure for only six months. On admission: Orthopnea, anasarca, dilated heart, gallop rhythm, liver not made out an account of ascites. At time of test, firm liver edge palpable three fingers' breadth below costal margin. Same symptoms as on admission but less marked. Impression: Moderate recent chronic passive congestion of liver and no evidence of chronic lesion. Blood examination: Hb., 75 per cent; R. B. C., 6,600,000. April 27, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 32 per cent. On May 7, liver no longer felt. Symptoms have cleared up.

(42.) J. J., age 44, male, colored.

Clinical diagnosis: Myocardial insufficiency, syphilis, aortic insufficiency. Very severe break in compensation. General edema; edema of lungs. Dilated heart. Very large tender liver. Several previous breaks. In extremis at time of both tests. April 22, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 5 per cent. May 19, 1913, injected 300 mg. Amount in urine, 0. Amount in stools, 24 per cent. *Autopsy*: 3946. Diag.—Syphilis, aortitis, aortic stenosis and insufficiency, myocarditis, chronic passive congestion of lungs and abdominal viscera, etc. Liver weighs 1220 gm. The microscopical section shows well marked passive congestion with central atrophy, obviously of long duration. The liver cells in many lobules have completely disappeared, leaving only a thickened reticulum. The lobulation is slightly irregular. Fatty degeneration appears in the middle zone. About one-half of the parenchyma cells nearly normal. Some of the lobules show the bile canaliculi distended with yellow, hyaline plugs. This condition is present in the central portion of the lobules, and absent in the periphery.

(43.) No. 89247. T. G., age 52, male, colored.

Clinical diagnosis: Arteriosclerosis, myocardial degeneration, chronic nephritis. Shortness of breath, palpitation, nycturia, transient swelling of feet and ankles for five months. Examination: Relative cardiac dullness 17 cm. to left, 5.5 to right, arrhythmia. No myocardial insufficiency. Liver dullness to one finger's breadth above costal margin; edge not felt. No evidence of liver disease. Blood examination: Hb., 72 per cent; R. B. C., 4,600,000. May 17, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 30 per cent. May 24, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 28-30 per cent. Thrombosis at site of injection.

(44.) No. 89149. I. W., age 48, male, colored.

Clinical diagnosis: Mitral insufficiency. Arteriosclerosis. Old mitral insufficiency. History of a break in 1910. Now for past two months, dyspnea, cough, palpitation. Examination: R. C. D., 15 cm. to left in sixth interspace, loud systolic murmur, slight edema of lungs, none of ankles. Liver to costal margin; edge not definitely felt. Nothing to indicate liver injury. Blood examination: Hb., 78 per cent; R. B. C., 5,000,000. May 22, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 28 per cent.

(45.) No. 89301. I. B., age 26, male, white.

Clinical diagnosis: Miliary tuberculosis. Tuberculous pericarditis. Liver not below costal margin. Edge not felt. Slight irregular fever. Blood examination: Hb., 60 per cent; R. B. C., 5,200,000. May 27, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 21 per cent. *Autopsy*: 3941. Tuberculous pericarditis. Miliary tuberculosis of lungs, liver and spleen. Ascites, hydrothorax, chronic passive congestion of viscera, etc. Liver weight 1775 gm. The microscopical section shows well marked passive congestion with atrophy of the central portion of the lobule. About two-fifths of the parenchyma is involved in the central atrophy. There is little fatty degeneration. The margin of the parenchyma is normal.

(46.) No. 89417. S. R., age 33, female, colored.

Clinical diagnosis: Myocardial insufficiency, syphilis, aortic insufficiency. At time of first test marked broken compensation with anasarca. Edema of lungs. Liver hard, tender, down almost to umbilicus. At second test condition improved but still hard liver a palm's breadth below costal margin. Impression: Probably marked nutmeg liver. No signs of hepatic insufficiency. April 24, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 7 per cent. May 8, 1913, Amount in urine, 0. Amount in stools, 33 per cent.

(48.) J. M., age 40, male, colored.

Clinical diagnosis: Myocardial insufficiency, syphilis, aortic insufficiency. Several previous breaks. At time of test slight edema of ankles and lungs, dyspnea, enlarged heart. Liver four fingers' breadth below costal margin and hard. Impression: Moderate induration of liver. No signs of hepatic insufficiency. June 19, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 20-22 per cent.

(49.) No. 88072. J. N., age 52, male, white.

Clinical diagnosis: Cirrhosis of liver. *First admission* in 1907: Long alcoholic history. At that time for 19 weeks dropsy, "misy in stomach," and constipation. Blood in stools. Tapped six times before admission, one "gallon" removed each time. Heart and lungs clear. Liver edge 2.5 cm. below ensiform. Edge uneven and firm. Ascites and edema of legs. Tapped 27 times between March, 1907, and October, 1907. Total of 272 L. removed. Discharged. Improved. Abdomen still slightly swollen and some edema of legs. No fever, leucocytosis, drowsiness, or any signs of hepatic toxemia. Symptoms due apparently more to portal obstruction than to liver insufficiency. *Second admission, June, 1911*. Meanwhile tapped three to four times, but no other symptoms. Felt well. Returned on account of increase in size of abdomen and sharp pains below costal margin. Slight jaundice for one year. Heart and lungs clear. Liver edge 3 cm. below costal margin. Tenderness in gall bladder region, with rigidity of recti. Increased dullness in gall bladder region. Slight jaundice. Movable dullness in flanks. W. B. C., 14,000. Irregular fever up to 100° F. No note of tapping during this admission. Discharged July 5. Temperature normal, feeling well, no shifting dullness. Levulose test by Dr. Churchman. Positive on 100 gm. *Third admission*. Recalled to have test made. Good health since 1911. Complaints only of occasional slight dyspnea. Is able to work. Abdomen pendulous, walls soft and flabby. Relative hepatic dullness begins in fifth interspace and absolute hepatic dullness in sixth interspace. Dullness to 3 cm. below costal margin in right mamillary line. Edge felt firm but regular. No ascites. No dilated superficial veins. No edema of extremities. Heart and lungs clear. Urine clear. No fever. Impression: Undoubted cirrhosis of liver. Never any symptoms to suggest hepatic insufficiency except perhaps on second admission. Symptoms due to portal obstruction which at present is perfectly compensated. Blood examination: Hb., 75 per cent; R. B. C., 4,500,000. March 10, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 23 per cent. Fibrinogen content of blood by Dr. Whipple normal.

(50.) Bay View. D. M., age 56, male, white.

Clinical diagnosis: Cirrhosis of liver. Shortness of breath 20 years. Periodic edema of ankles. Markedly alcoholic. For three years, swelling of abdomen and epigastric pains. At time of test general bronzing. Patient is torpid and dull. Liver, 4 cm. below costal margin in right mamillary line. Superficial veins dilated. Caput medusae. Edge of liver firm. Spleen palpable. Very slight ascites. March 26, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 6 per cent. No autopsy.

(52.) Surg. No. 31832. K. F., age 48, female, white.

Clinical diagnosis: Carcinoma of stomach, metastases to liver. For two months chills, sweating, fever, pain in epigastrium, radiating to right shoulder, vomiting and loss of weight. Liver dullness from third interspace. Firm, smooth rounded liver edge palm's breadth below costal margin. Surface smooth. *Exploration*: Liver enormously enlarged, studded with large carcinomatous nodules. No symptoms of hepatic insufficiency. No glycosuria. March 19, 1913, injected 400 mg. Amount in urine 1.5 per cent. Amount in stools 8 per cent. *Autopsy*: 3903. Carcinoma of pylorus. Metastases to liver. Atrophy and focal necrosis of liver parenchyma with fatty degeneration. Practically entire liver tissue involved. The microscopical section shows numerous



tumor nodules. Medullary cancer. Liver lobules show central, fatty degeneration and scattered areas of hyaline necrosis. In some areas these areas of necrosis are very extensive; in other lobules absent. The liver parenchyma adjoining cancer growth shows extreme atrophy and fatty degeneration.

(53.) Bay View. A. H., age 67, female, white.

Clinical diagnosis: Carcinoma of gall bladder. Cholelithiasis. Six or seven attacks of jaundice in past 40 years. Two weeks before admission—weakness, loss of appetite, jaundice. Examination: Emaciation, moderate jaundice, large mass, firm and rounded, from right costal margin down to 4 cm. below level of umbilicus (gall bladder?). Liver edge well felt; smooth, normally firm. Wassermann reaction 100 per cent +. Blood examination: Hb., 55 per cent. April 22, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 18 to 20 per cent. Two and one-half months after onset jaundice more intense than ever.

(54.) No. 88424. E. S., age 33, male, white.

Clinical diagnosis: Cancer of stomach (metastases). For two months attacks of vomiting, nausea and pain following about two hours after eating. For past week vomitus bloody. Lost 80 pounds in three months. Examination: Emaciation; anemia; firm, nodular, transverse mass in epigastrium, thought by some to be liver, but finally was thought to be stomach or omentum. Liver dullness only to costal margin. Edge not felt. Blood examination: Hb., 38 per cent; R. B. C., 3,600,000. March 31, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 4 per cent. Stools unsatisfactory. April 8, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 22 per cent. Good specimens. Exploration: Carcinoma of stomach, metastases in glands and omentum. Liver smooth, no nodules made out (Finney). Death.

(56.) No. 87656. M. S., age 40 (?), female, colored.

Clinical diagnosis: Carcinoma of cervix uteri. One month before test general abdominal carcinomatosis found on abdominal exploration. At time of test some ascites; irregular nodular masses. Impression was that none of these were connected with liver, that dullness came to costal margin and that edge was not felt. Blood examination: Hb. 40 per cent; R. B. C., 4,300,000. March 5, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 39 per cent. Discharged April 10, 1913, without marked change in condition.

(57.) No. 89781. J. T., age 45, male, white.

Clinical diagnosis: Primary cancer of liver. For two months weakness, loss of weight, abdominal pain. *Exploratory laparotomy*: extensive inoperable primary cancer of liver. At time of test (post operative) great weakness and emaciation. Hb., 88 per cent. June 20, 1913 injected 400 mg. Amount in urine, trace. Amount in stools, 6 to 7 per cent.

(58.) No. 87933. M. B., age 27, male, white.

Clinical diagnosis: Suspected amebic abscess of liver. Ill about two months. Septic fever up to 102° F. W. B. C., 12,000. Liver dullness from fifth interspace to 6 cm. below costal margin in right mammillary line. Edge blunt, round. Surface smooth and tender. Careful exploration March 19 by Dr. Hulstet "was negative, with the exception of the enlargement of the right lobe of the liver, and the finding of a few adhesions between the right lobe and the dome of the liver." The peritoneum at "the lower portion of the right lobe which presented in wound was very soft and almost fluctuant." Blood examination: Hb. 75 per cent; R. B. C., 4,000,000. March 10, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 33 per cent. Death. No autopsy.

(60.) No. 88925. F. R., age 40, male, colored.

Clinical diagnosis: Hepatitis, periostitis, syphilis, tuberculosis (?) tuberculous peritonitis (?) and perihepatitis (?). Ascites of obscure origin, large hard spleen. No evidences of collateral cir-

culatation. Liver just felt at costal margin, indefinite, not hard. Impossible to tell extent of anatomical liver change. No clinical signs of hepatic insufficiency. Blood examination: Hb., 40 per cent; R. B. C., 2,600,000. April 27, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 30 per cent. Case not followed after leaving hospital.

(61.) No. 88861. E. P., age 19, male, colored.

Clinical diagnosis: Tuberculosis (eye test). Splenomegaly. Liver easily felt one finger's breadth below costal margin; edge smooth and firm. Spleen easily felt; edge firm and sharp. Diagnosis not clear; chronic malarial infection suspected. No parasites found. No clinical signs of hepatic insufficiency. Blood examination: Hb., 90 per cent; R. B. C., 5,000,000. May 10, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 23 per cent.

(62.) No. 89082. J. McC., age 52, male, white.

Clinical diagnosis: Tuberculous peritonitis? Hepatitis? Syphilis (w). Mitral insufficiency. Arteriosclerosis. Symptoms: For about a month weakness, shortness of breath, abdominal pain, swelling of feet. On admission, mitral murmur, heart 11 cm. to left, liver one finger's breadth below costal margin; edge not felt, edema of legs, ascites. Diagnosis not clear; most likely cause of findings is myocardial failure, perhaps with chronic peritonitis. No symptoms of hepatic insufficiency. Blood examination: Hb., 60 per cent; R. B. C., 4,400,000. May 17, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 31 per cent. June 10, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 31 per cent.

(63.) No. 89439. J. K., age 56, male, colored.

Clinical diagnosis: Acute cholecystitis. Previously well. Acute onset with nausea, pain below right costal margin. Rigidity of upper right rectus, slight icterus. Leucocytosis, 22,000. Rapid recovery. Blood examination: Hb., 70 per cent; R. B. C., 4,000,000. May 29, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 30 per cent.

(64.) No. 89593. H. A., age 52, male, white.

Clinical diagnosis: Tuberculous peritonitis (?). Cirrhosis of liver (?). For six months increasing weakness and abdominal pain, with gradual ascites. Hemorrhoids 8 years. Emaciation, anemia, ascites, paracentesis—cloudy, brownish fluid, specific gravity 1017. Liver felt almost at umbilicus; surface irregular, firm, and slightly tender. June 3, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 22 per cent.

(65.) Bay View. E. T., age 33, male, colored.

Clinical diagnosis: Syphilitic liver, syphilitic endarteritis, mitral insufficiency. Very large liver reaching to level of umbilicus in right flank, slightly irregular, and knobbed. Slightly tender. No other masses. Ascites. April 22, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 18 to 22 per cent.

(66.) Bay View. G. A. S., age 27, male, colored.

Clinical diagnosis: Syphilitic hepatitis? Amyloid? Pulmonary tuberculosis. Definite primary and tertiary lesions with positive Wassermann reaction. Two months before admission: swelling of legs, shortness of breath, cough and expectoration. Examination: Ascites, liver very large, smooth, not tender, does not pulsate, 8 cm. below costal margin. Moderate, irregular fever up to 101° F. in afternoon. Hb., 75 per cent. April 22, 1913, injected 400 mg. Amount in urine, 0. Amount in stools, 40 per cent. Autopsy: B. V. 41. Liver.—Microscopical section shows well-marked passive congestion, with central atrophy involving about 1/4 of each lobule, where the liver cells have undergone advanced atrophy, and in some instances even complete death. The sinusoids are engorged with blood. The liver lobulation is quite regular. Kidneys show advanced chronic nephritis. Lungs.—Bronchiectasis and organizing bronchopneumonia.



## TESTS FOR HEPATIC FUNCTION AND DISEASE UNDER EXPERIMENTAL CONDITIONS.

## PHENOLTETRACHLORPHTHALEIN.

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In an earlier paper (Whipple, Mason and Peightal)<sup>1</sup> we have called attention briefly to three tests which may be of value in determining liver injury and estimating liver functional capacity. The estimation of blood plasma or serum *lipase* will determine the presence of acute liver injury when this ferment *lipase* increases greatly (five or eight times normal). It does not, however, give an accurate idea of the amount of acute liver injury, although a grave injury will show a higher *lipase* reading than a moderate injury. The test is of value as a qualitative rather than as a quantitative test and is of importance in suspected eclampsia, chloroform poisoning, yellow atrophy, cholangitis, etc.

*Fibrinogen* is a second factor of importance, and when this element of the blood plasma is very low it gives certain evidence of a grave hepatic insufficiency; but it may not be low in all types of liver cirrhosis. A rough estimate of the fibrinogen content in the blood can be made very easily by clotting a little plasma with calcium and testing the toughness of the clot with a glass rod, if possible with a normal control and fractional dilutions. With practice it is very easy to determine whether the fibrinogen is greatly diminished in amount, when quantitative estimates can be made if desirable.

*Phenoltetrachlorophthalein* has been studied especially by Abel and Rowntree<sup>2</sup> who have determined its physiological and therapeutic properties. Through their kindness we have been able to use this drug in our work with various experimental liver conditions. The experimental work detailed below will show that this drug, when given intravenously and collected in the feces and urine, can give important evidence concerning the amount of liver injury and the degree of functional impairment.

It will be found that after an acute liver injury there is an immediate drop in liver phthalein output in the feces and this drop corresponds very closely to the degree of injury, falling to zero with a fatal intoxication. Further, this phenoltetrachlorophthalein, which does not come through in the urine of a normal dog, will appear very promptly in the urine after the liver injury is established. It seems probable that the phthalein is so modified by contact with the injured liver cell that it can pass the kidney filter which is impermeable to the unchanged phthalein. As the injury to the liver is repaired the curve of phthalein output in the feces will rise to normal and the urine output sinks to zero.

## METHOD.

The various methods for producing liver injury are described under the various experiments. The routine followed in giving the phthalein may be outlined as follows: As a rule the experi-

ments were done in groups, three to six animals being injected at the same time, at least one normal dog serving as control. When a dog weighs less than 20 pounds, 0.1 gm. phthalein is given as a rule, and 0.2 gm. of the drug when over 20 pounds. Subcutaneous injection does not give uniform results. Practically all these injections were given by means of a needle introduced into the jugular vein, and with care this procedure can be repeated very frequently without causing thrombosis. Laceration of the vein may predispose to a localised thrombus involving perhaps only one or two inches of the vein. Injection is usually done about 11 a. m. or 5 p. m. and followed by about 200 cc. of water by stomach tube to promote diuresis. Urine is collected usually by a catheter or from a clean metabolism cage at 5 p. m. or the following morning and a purge given, usually magnesium sulphate or croton oil. Feces are collected at the end of 20-24 hours and the feces subsequently passed are collected to insure complete phthalein collection. With brisk purgation the second fraction will rarely contain more than a trace of phthalein. When purgation is not brought about because of vomiting or other factors the feces on the second or third day may contain the usual amount of phthalein, but there may be some loss, perhaps from absorption or destruction. It is not safe to draw deductions from a slightly lowered output under these circumstances.

The method of extracting the phthalein from the feces has been modified from time to time as the work progressed and the following method in our hands gives the most uniform results working with dog feces. The determinations were done as a rule in triplicate, each worker using a separate fraction of the feces emulsion and making independent readings. When the readings were not uniform, repeated determinations were done, but it was unusual for the readings to vary more than 5 per cent. The feces must be collected carefully from metabolism cages, the residue being washed out with a wash bottle and spatula to remove the last traces. The total feces are diluted to one or two litres as may be necessary in the collection and washing. The mixture is made alkaline with 10 cc. sodium hydrate (40 per cent) and shaken until a uniform mixture is obtained. If there is any doubt of this a second determination the following day is advisable when solution is complete. One-tenth of this mixture is taken and diluted to 500 cc. with water and 3-4 cc. sodium hydrate. After shaking and sedimentation over night this second solution may be perfectly clear, and with filtration and dilution can be read directly in the colorimeter. When no precipitation is needful we believe the readings to be most accurate, and have used such solutions to control the methods of precipitation which at times remove some of the phthalein. Under such circumstances the basic lead acetate precipitation may drop the reading in parallel observations as much as 5-10 per cent and we must assume that the lead acetate may hold some of the phthalein, even in alkaline solution.

The second fraction, as a rule, must be cleared before a suitable reading can be made. Of the 500 cc. solution 100 cc. are taken for precipitation with 4-5 cc. of a calcium solution (calcium chloride 90 gm., ammonium hydrate (conc.) 10 cc. and water to 500cc.). This throws down an abundant precipitate on shaking and the mixture is made up to 200 cc. with 3 to 4 cc. sodium hydrate and water. After standing and filtration a perfectly clear solution is obtained which can be read directly against a standard

solution of phthalein, 10 mg. to 1 litre. In some feces, normal or otherwise, this extraction will give a dirty, reddish color, which is difficult to read in the colorimeter, but varying the amounts of the calcium reagent and sodium hydrate will usually give a clear lavender red tint which can be estimated accurately. At times a solution may be cleared up after filtration by adding a little more sodium hydrate and standing several hours.

The estimation of phthalein in the urine is very simple:—addition of a little hydrate and calcium solution with dilution to a proper degree for reading. The normal dog often excretes traces of phthalein in the urine sufficient to give a rose red with alkali, but not sufficient for a reading. When phthalein to the extent of 0.2 per cent or more is excreted in the urine, we believe it indicates liver injury. Bile pigments give difficulty, but the addition of calcium with removal of the precipitated bile pigments will give a solution suitable for the colorimeter.

## EXPERIMENTAL OBSERVATIONS.

## FATAL CHLOROFORM POISONING AND LIVER NECROSIS.

Dog 12-50.—Fox terrier, female; weight 17 lbs.

April 1. 1 p. m., *phthalein 0.1 gm.* intravenously. Weight 17½ lbs. 4 p. m., urine contains no phthalein.

April 2. Feces abundant. *Phthalein 35-40 per cent.*

April 12. Dog in excellent condition; weight 18 lbs. 12 m., *phthalein 0.1 gm.* intravenously.

April 13. Abundant feces. *Phthalein 45 per cent.*

April 15. 1 p. m., *phthalein 0.2 gm.* intravenously. Weight 19½ lbs. 4 p. m., urine contains traces of phthalein.

April 16. Abundant fluid feces. *Phthalein 40 per cent.*

May 20. Dog is in a good condition, weight 18½ lbs. *Chloroform anaesthesia for three hours.*

May 21. 11 a. m., *phthalein 0.1 gm.* intravenously. Dog appears rather sick and intoxicated. 5 p. m., urine by catheter contains abundant *phthalein, 8 per cent.*

May 22. 11 a. m., abundant feces and vomitus contains only faint traces of phthalein. Dog shows definite icterus of the skin and mucous membranes and appears very sick, dull and drowsy. Weight 15½ lbs. Urine by catheter contains traces of phthalein. 11.30 a. m., *phthalein 0.2 gm.* intravenously. 1.30 p. m., death. Abundant feces were passed shortly before death. *Phthalein 9.* Autopsy done at once. Thorax and heart negative. Lungs show a few small purple patches of bronchopneumonia or atelectasis. Liver shows extensive central necrosis involving all the lobules. Microscopical section: The greater part of the liver has undergone complete hyaline necrosis, most of the injured liver cell nuclei having disappeared. Only a few rows of intact liver cells remain about the portal spaces and many of these cells show advanced fatty degeneration. Wandering cells of all descriptions are numerous in the areas of necrosis. The bile ducts are normal, but the larger ones in places are distended with colloid like material. The necrosis involves more than four-fifths of the liver parenchyma of each lobule. This is a typical example of fatal

delayed chloroform poisoning. In places there are subserous hæmorrhages, particularly in the pelvis and about the bladder.

Intestinal contents removed carefully. Phthalein present only in traces. Gall bladder contains only the faintest trace of phthalein.

## CHLOROFORM POISONING, SEVERE AND MILD.

Dog 12-48.—Small fox terrier, female; weight 14 lbs.

April 3. 12 m., *phthalein 0.1 gm.* intravenously. 5 p. m., urine contains no phthalein.

April 4. Abundant feces. *Phthalein 47 per cent.* Urine contains no phthalein.

April 8. 11 a. m., *chloroform anaesthesia for 1½ hours.* At the end of the anaesthesia intravenous injection of *phthalein 0.1 gm.* 5 p. m., vomitus abundant. *Phthalein 12 per cent.*

April 9. No feces. Urine soiled with some vomitus and contains phthalein 0.1 per cent. Dog appears quite sick.

April 10. 10 a. m., night urine contains traces of phthalein. One fluid stool. *Phthalein 7-9 per cent.* 12 m., urine contains no phthalein, but abundant bile pigment. 3 p. m., *phthalein 0.1 gm.* intravenously; weight 11½ lbs.

Plasma Lipase .10-.10 Initial alkalinity.

1.10-1.30 Butyric acidity.

1.20-1.40 Acid production.

Plasma clots are decidedly soft and fibrinogen estimated at about 100 mps., which is about 25 per cent of normal. 5 p. m., urine contains abundant phthalein 1½ per cent. 7 p. m., urine contains phthalein 1 per cent. 9 p. m., urine plus vomitus contains phthalein 1½ per cent.

April 11. 9 a. m., vomitus and urine of night, phthalein 2 per cent. 3 p. m., urine contains faint traces of phthalein. No feces. 4 p. m., two-third fluid stools following croton oil. Phthalein 25 per cent.

April 12. Dog is improving rapidly and eats well.

April 15. 1 p. m., *phthalein 0.1 gm.* intravenously; weight 12½ lbs. 4 p. m., urine contains phthalein 0.1 per cent.

April 16. 10 a. m., abundant fluid feces. *Phthalein 45 per cent.*

May 28. Dog is in excellent condition and weighs 12 lbs. 5 p. m., *Phthalein 0.1 gm.* intravenously.

May 29. Urine contains no phthalein. Feces contain 40-44 per cent.

May 30. Abundant fluid feces contain no phthalein.

June 2. 3 p. m., *chloroform anaesthesia 1 hour.*

June 3. Dog seems normal; weight 11 lbs. 11 a. m., *phthalein 0.1 gm.* intravenously.

Plasma Lipase .10-10 Initial alkalinity.

.60-50 Butyric acidity.

.70-60 Acid production.

5 p. m., urine contains phthalein 1½ per cent. but no bile pigments.

June 4. No feces. Dog is normal.

June 5. Abundant feces. Phthalein 43 per cent.

TABLE I. DOG 12-50.—CHLOROFORM POISONING.

Date.	Phthal- ein given.	Phthalein excreted.		Liver injury.	Weight.	Remarks.
		Feces.	Urine.			
		<i>Per cent.</i>	<i>Per cent.</i>		<i>Pounds.</i>	
Apr. 1	.100	40	0	....	17½	Normal.
12	.100	45	0	....	18	Do.
15	.200	40	Traces.	....	19½	Do.
May 20	....	....	....	Chloroform 3 hrs.	....	....
21	.10	Traces.	8	....	18½	Ferretic material.
22	.200	do.	(?)	....	15½	Liver lobules & necro- sis.
	Death	in bile.	....	....	....	....

TABLE II. DOG 12-48.—CHLOROFORM POISONING.

Date.	Phthal- ein given.	Phthalein excreted.		Liver injury.	Weight.	Remarks.
		Feces.	Urine.			
		<i>Per cent.</i>	<i>Per cent.</i>		<i>Pounds.</i>	
Apr. 3	.100	47	0	....	14	Normal.
8	.100	20	0	Chloroform 1½ hrs.	11½	Phthalein given at end of anaesthesia.
	.100	25	4	....	11½	Lipase 5 times normal.
	.100	45	0.1	....	12½	....
May 28	.100	44	0	....	12	Dog normal.
June 2	....	....	....	Chloroform 1 hr.	....	....
3	.100	43	1.5	....	11	Lipase 3 times normal.

The two preceding experiments (Dogs 12-50 and 12-49) show the prompt drop in phthalein output in the feces. In the first experiment there is a drop from 40 per cent excretion to a mere trace in a fatal chloroform poisoning, and in the second a prompt drop from 47 per cent to 20 per cent and 25 per cent with recovery to 45 per cent following repair of the liver injury within one week. The urine phthalein rose from zero, which is normal, to 8 per cent in the fatal case and to 4 per cent in the case with recovery. In the second experiment a slight degree of liver injury produced by one hour chloroform anaesthesia caused no drop in the phthalein of the feces, but an output of  $1\frac{1}{2}$  per cent in the urine and a rise in plasma lipase. From the last two observations we may conclude that this short chloroform anaesthesia caused actual liver injury, but did not upset the functional capacity of the liver. This corresponds with the clinical observations of this animal.

The following experiment (Dog 12-78) shows the same prompt drop in phthalein output in the feces due to a chloroform anaesthesia of two hours. The drop was from 53 per cent to 30 per cent and finally to 20 per cent, with complete recovery in two weeks to 46 per cent. The dog was then poisoned fatally with phosphorous and died on the fourth day after the last dose. The phthalein output in feces fell to zero on the day before death, but the urine output rose from zero to  $4\frac{1}{8}$  per cent. The curve of phthalein excretion in the feces shows in a striking manner (Chart I).

#### CHLOROFORM AND PHOSPHOROUS POISONING.

Dog 12-78.—Large bull-dog, female; weight  $38\frac{1}{2}$  lbs.

April 1. 1 p. m., phthalein 0.2 gm. intravenously. 5 p. m., urine by catheter contains traces of phthalein.

April 2. Abundant feces. Phthalein 50-53 per cent.

April 21. 3 p. m., chloroform anaesthesia 1 hour 50 minutes.

April 22. Dog seems practically normal; weight 39 lbs. 12 m., phthalein 0.2 gm. intravenously. Blood plasma appears normal except for slight icteric tint. Clots in 7 minutes with the formation of a firm clot.

Plasma Lipase .10-.10 Initial alkalinity.

1.10-1.35 Butyric acidity.

1.20-1.45 Acid production.

5 p. m., urine by catheter contains bile. No albumin. Phthalein  $2\frac{1}{2}$  per cent.

April 23. Abundant feces. Phthalein 30 per cent. Dog has vomited a few times and this is the only sign of intoxication.

April 25. 11 a. m., dog is active and normal. Phthalein 0.2 gm. intravenously. 4 p. m., urine contains phthalein 1 per cent.

April 26. Abundant feces. Phthalein 19-20 per cent.

May 9. Dog in excellent condition; weight 37 lbs. 12 m., phthalein 0.2 gm. intravenously.

May 10. 10 a. m., one solid stool. Phthalein 23 per cent.

May 11. 1 soft stool. Phthalein 20-26 per cent. 1 p. m., phosphorous 10 mgs. in oil given subcutaneously.

May 12. Dog looks rather sick.

May 14. Dog has vomited food. Icterus is not present.

May 15. Dog appears better. Phosphorous 10 mgs. in oil given subcutaneously.

May 16. Dog appears pretty well.

May 18. Dog is quite sick, refuses food and vomits. Slight

icterus noted in the sclerae. 1 p. m., phthalein 0.2 gm. intravenously.

May 19. 9 a. m., dog found dead, but quite warm. Urine beneath cage (150 cc.) very concentrated and contains large amounts of bile pigments. Phthalein 4 per cent. Urine in bladder at autopsy 20 cc. Phthalein  $\frac{1}{2}$  per cent. Autopsy shows slight pleural effusion and bilateral hemorrhage pneumonia and edema. Oedema well marked in mediastinal tissues. Entire contents of the intestinal tract collected and washed from intestinal mucosa with care. Phthalein present in *merest trace*. Bile and gall bladder contain traces of phthalein perhaps a fraction of 1 per cent.

Liver in gross shows conspicuous lobulation and evidence of fatty change. Microscopical section: All the liver cells show fatty degeneration and contain medium and small-sized fat droplets. Necrotic liver cells scattered everywhere throughout the lobule are numerous. The portal tissues are rather edematous and filled with wandering cells, some of which contain a yellow granular pigment. The capillaries between the strands of liver cells are engorged with blood cells and phagocytes; wandering cells of every description are numerous. Occasional mitotic fig-

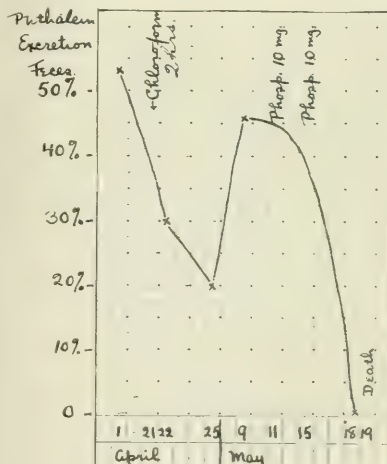


CHART I. Dog 12-78.—Chloroform and Phosphorous Poisoning.

TABLE III. Dog 12-78.—CHLOROFORM AND PHOSPHOROUS POISONING.

Date.	Phthalein given.	Phthalein excreted.		Liver injury.	Weight.	Remarks.
		Feces.	Urine.			
		Per cent.	Per cent.		Pounds.	
Apr. 1	.200	53	..	..	38½	Normal.
21	..	30	..	Chloroform 2 hrs.	39	Lipase 5 times normal.
25	.200	20	..	..	39	Recovery rapid.
May 9	.200	46	..	..	37	Purgation delayed.
11	..	23	..	Phosph. 10 mg.	..	Dog vomits constantly.
15	..	20-26	..	Phosph. 10 mg.	..	Death—bile phthalein, 4 per cent.
18	.200	..	4½	..	..	..
19	..	Intestinal traces.	..	..	..	..

ures are seen in liver cells. The bile canaliculi are not conspicuous. This is an excellent example of a subacute type of phosphorous injury to the liver. The irritant type of hemorrhagic bronchopneumonia associated with oedema is quite common in dogs given an overdose of phosphorous.



## SEVERE PHOSPHOROUS POISONING.

April 1. 1 p. m., *phthalein* 0.1 gm. intravenously. 5 p. m., urine by catheter shows very faint trace of *phthalein*.

April 2. Feces abundant. *Phthalein* 45 per cent.  
May 13. 3 p. m., *phthalein* 0.1 gm. intravenously. 8 p. m., urine contains no *phthalein*.

May 14. Abundant feces. *Phthalein* 47 per cent. Fowler's solution 2½ cc. given by stomach tube.

May 15. Dog has vomited and acts rather sick.  
May 16. Given ¼ grain morphia followed in two hours by 3 cc. of Fowler's solution by stomach. Weight 18 lbs.

May 23. 5 p. m., dog does not appear poisoned; weight 18 lbs. *Phosphorous* 5 mgs. given in oil subcutaneously.

May 28. Dog seems pretty well; weight 18 lbs. 5 p. m., *phthalein* 0.1 gm. intravenously.

May 29. Urine of previous night contains no *phthalein*, which speaks against any definite injury by the dose of phosphorous given five days previously. Abundant feces collected in the afternoon. *Phthalein* 45-50 per cent.

May 30. 4 p. m., *phosphorous* 7.5 mgs. given subcutaneously. Weight 16 lbs. Feces passed during the night abundant. *Phthalein* 2-3 per cent.

June 2. Dog looks pretty well, weight 17 lbs. Icterus noted for the first time in sclerae and skin, indicating fatal poisoning as a rule. 11 a. m., *phthalein* 0.1 gm. intravenously. 3 p. m., urine contains much *phthalein*. 4½ per cent. Dog vomits repeatedly but the vomitus contains no bile, being made up chiefly of clear fluid and mucus. 5 p. m., urine contains abundant *phthalein*, 1½ per cent. Bile is very abundant.

June 3. 10 a. m., urine and vomitus below cage contain traces of *phthalein*. 10 a. m., abundant fluid feces. *Phthalein* present in only the faintest traces, impossible to read in ten times the usual concentration. Jaundice of skin is quite deep. 12 m., urine contains abundant bile. *Phthalein* 0.1 per cent. ±.

June 4. 10 a. m., soft feces contain mere traces of *phthalein*. General condition is unchanged. Dog is steadily losing weight; weight 15 lbs. 12 m., *phthalein* 0.2 gm. intravenously. 3 p. m., urine contains abundant *phthalein*, 3 per cent. 4 p. m., urine contains *phthalein*, 3½ per cent. Night urine contains *phthalein*, 2-4 per cent. Bile is constantly present.

June 5. 9 a. m., fresh urine contains *phthalein*, 0.7 per cent. Dog does not vomit and drinks considerable water; weight 15 lbs. 2 p. m., abundant fresh urine contains much bile and *phthalein*, 1 per cent.

June 6. 11 a. m., condition is about the same; weight 14½ lbs. Night urine contains a good deal of *phthalein*. 12 m. 500 cc. of normal saline subcutaneously. 3 p. m., soft soapy looking feces passed and contain small amounts of *phthalein*. 1¼ per cent. Urine contains traces of *phthalein*. Jaundice remains intense, but dog drinks milk and does not vomit.

June 7. 10 a. m., clean urine contains definite traces of *phthalein* and much bile. Dog is improving; weight 15½ lbs. 12 m., urine is rich in bile and contains only traces of *phthalein*.

June 8. 10 a. m., urine contains much bile and faint traces of *phthalein*. Feces are abundant, gray and putty like. *Phthalein* 0; not the faintest trace. Icterus is becoming less intense.

June 9. 10 a. m., urine of night contains no *phthalein*; gives only faint test for bile pigments. Dog is quite lively and eats well; weight 16 lbs. 12.30 p. m., *phthalein* 0.2 gm. intravenously. 4 p. m., urine contains *phthalein*, 1½ per cent. 5 p. m., urine contains *phthalein*, 0.6 per cent.

June 10. 10 a. m., urine of night contains only faint traces of *phthalein*. Abundant feces collected in afternoon. *Phthalein* 33 per cent. Jaundice is clearing completely in skin and only faint traces in the sclerae. 4 p. m., *phthalein* 0.1 gm. intravenously.

June 11. 10 a. m., urine of night contains *phthalein*, 1 per cent. 3 p. m., abundant feces. *Phthalein* 22 per cent. Dog seems almost normal, and the urine is quite free from bile.

June 16. Appearance normal; weight 16¾ lbs. Urine is free from pigment.

July 10. 10 a. m., dog appears well; weight 15¾ lbs. *Phthalein* 0.1 gm. intravenously. 5 p. m., urine, *phthalein* 0.3 ± per cent.

July 11. Abundant feces. *Phthalein* 60 per cent (Hypersecretion?).

July 14. Dog as usual; weight 16 lbs. Sacrificed. Autopsy at once. All the organs are normal in gross. The bile papilla and bile ducts are normal. The gall bladder shows thickening and slight ulceration in its distal portion, with adherent slimy green material on the mucous surface. There are adhesions between the liver and omentum at this place. Liver on section

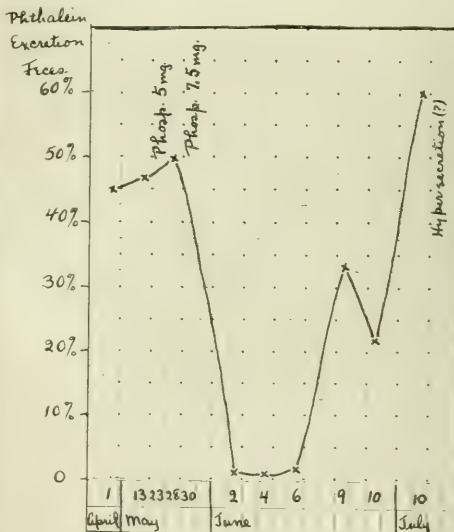


CHART II. Dog 12-53.—Phosphorous Poisoning and Repair.

TABLE IV. Dog 12-53.—PHOSPHOROUS POISONING.

Date.	Phthalein given.	Phthalein excreted.		Liver injury.	Weight.	Remarks.
		Feces.	Urine.			
		Per cent.	Per cent.		Pounds.	
Apr. 1	.100	45	0	....	16½	Normal.
May 13	.100	47	0	....	18	Do.
14	....	..	..	Fowler's Sol.	....	
16	....	..	..	Fowler's Sol.	18	
23	.100	..	..	Phosph. mg.	18	
28	.100	50	0	Phosph. 7.5 mg.	16	
30	....	..	..	....	17	Icterus.
June 2	.100	..	6	....	15	Bile + + + in urine.
3	....	Traces.	+	....	15	Vomiting and prostration, dull and drowsy.
4	.200	0	½	....	15	
5	....	..	1.7	....	14½	Given 500 cc. salt infusion.
6	....	1½	+	....	15½	
7	....	0	+	....	16	Bile + + + in urine.
8	....	0	Traces.	....	16	Bile traces in urine.
9	....	0	0	....	16	Dog eats and is lively.
9	.200	33	2	....	16	Dog improving rapidly.
10	.100	32	1±	....	16	
10	.100	32	1±	....	16	
July 10	.100	60	0.3±	....	15½	Hypersecretion (?).

1 A. M.

2 P. M.

seems normal. Microscopical section: Normal liver parenchyma except for a slight increase in phagocytes about the portal areas. Some of these phagocytes contain yellow pigment. The repair is almost perfect.

The preceding experiment (Dog 12-53) illustrates the gravest type of phosphorous liver injury. The normal phthalein output was constantly 45-50 per cent, and after the phosphorous injury dropped to zero with a corresponding rise in the urine from zero to 6 or 9½ per cent. This is the only case in a considerable number of experiments where a dog recovered from phosphorous poisoning after a definite icterus had developed. The liver repair was considerably delayed in this instance, but finally after weeks the phthalein curve returned to normal and even showed evidence of hypersecretion (Chart II). Autopsy showed practically perfect repair of the liver injury.

#### PHOSPHOROUS POISONING—FATAL 6 DAYS.

Dog 12-88.—Fox terrier, male; weight 14½ lbs.

April 3. 1 p. m., *phthalein 0.1 gm.* intravenously. 5 p. m., urine contains no phthalein.

April 4. Abundant feces. Phthalein 43-47 per cent.

April 7. *Phosphorous 10 mgs.* in oil given subcutaneously; weight 14 lbs.

April 8. Dog shows no signs of intoxication. 12 m., *phthalein 0.1 gm.* intravenously. 5 p. m., urine by catheter contains traces of phthalein.

Plasma Lipase .10-.10 Initial alkalinity.

1.45-1.10 Butyric acidity.

1.55-1.20 Acid production.

April 9. Abundant feces. *Phthalein 25 per cent.* Dog is pretty sick and refuses food.

April 10. 3 p. m., *phthalein 0.09 gm.* intravenously. Blood plasma clots normally but the blood clot is decidedly flabby indicating a drop in fibrinogen.

Plasma Lipase .10-.10 Initial alkalinity.

.60-.50 Butyric acidity.

.70-.60 Acid production.

6 p. m., urine contains abundant phthalein, 1½ per cent. 9 p. m., urine contains phthalein, 2½ per cent.

April 11. Abundant feces. *Phthalein* shows the *merest trace*. Dog is sick and keeps very quiet.

April 12. Dog shows definite jaundice of skin and sclerae. 12 m., *phthalein 0.1 gm.*; weight 12½ lbs. 3 p. m., urine contains abundant bile. Phthalein 1 per cent.

April 13. Dog is very sick and has much bloody diarrhoea. No vomiting. Feces contain mere *traces of phthalein*. 3 p. m., dog very sick and was sacrificed. Autopsy performed at once. Blood clots formed soft jelly like masses indicating very little fibrinogen.

Plasma Lipase .10-.10 Initial alkalinity.

.65-.60 Butyric acidity.

.75-.70 Acid production.

Thorax, heart and lungs are normal. Spleen shows a few hemorrhages beneath the capsule. Stomach contains black, tarry material. Duodenum is normal. Bile can be squeezed with ease through the bile papilla. The gall bladder is small and flabby. The bile in the gall bladder contains phthalein 1 per cent ±. Urine in the bladder contains abundant bile pigments and phtha-

lein 2 per cent ±. There is a definite cloud of albumin. Kidneys show some linear abscesses, which are most numerous in the right kidney. Liver is pale and yellowish, obviously very fatty, quite soft and slightly smaller than normal.

Microscopical sections are negative except the liver. This shows advanced fatty degeneration, all the liver cells showing great numbers of fat droplets. The majority of them show a mere honeycombed protoplasm. Actual hyaline necrosis is rarely observed, but is present. Wandering cells are pretty numerous. The portal structures are normal.

TABLE V. DOG 12-88.—PHOSPHOROUS POISONING.

Date.	Phthalein given.	Phthalein excreted.		Liver injury.	Weight.	Remarks.
		Feces.	Urine.			
		Per cent.	Per cent.		Pounds.	
Apr. 3	.100	45	0	....	14½	Normal.
7	....	....	....	....	15½	....
8	.100	....	Trace.	Phosph. 10 mg.	15½	Dog appears well.
9	....	25	....	....	14½	Dog will not eat.
10	.090	....	4	....	14½	....
11	....	Traces.	1	....	12½	Dog is sick.
12	.100	....	1 ±	....	12½	Icterus.
13	....	Traces.	2 ±	....	....	....
	Sacrificed.	Bile 1 ±	2 ±	....	....	Fibrinogen very low.

The preceding experiment (Dog 12-88) shows a typical example of phosphorous poisoning and extreme liver injury. It will be seen that the phthalein output in the feces fell rather slowly from the normal 45 per cent to 25 per cent on the second day, but practically to zero on the fourth day, and remained here until death on the sixth day. It is interesting to note that the lipase readings were highest on the day following the injection of phosphorous and fell somewhat as the intoxication progressed. We have observed the same lipase curve in fatal chloroform poisoning.

#### CHRONIC PHOSPHOROUS POISONING.

Dog 12-105.—White bull dog, female; weight 24½ lbs.

April 18. 2 p. m., *phthalein 0.1 gm.* intravenously. 5.30 p. m., urine by catheter contains no phthalein.

April 19. Abundant feces. *Phthalein 32 per cent.*

April 22. 12 m., *phthalein 0.2 gm.* intravenously; weight 22½ lbs. 5 p. m., urine contains no phthalein.

April 23. Abundant feces. *Phthalein 39 per cent.*

May 23. Dog in good condition, weight 24 lbs. *Phosphorous 7½ mgs.* in oil given subcutaneously.

May 25. Dog looks somewhat intoxicated.

May 26. Dog appears sick but has no icterus; weight 22 lbs. 11 a. m., *phthalein 0.2 gm.* intravenously. 5 p. m., urine by catheter contains no bile. Phthalein 1.2 per cent.

May 27. Abundant feces. *Phthalein 22 per cent.*

May 28. Dog has diarrhoea and vomiting. Urine by catheter contains no albumin and no bile pigment.

May 30. 5 p. m., *phthalein 0.2 gm.* intravenously; weight 21½ lbs.

May 31. Feces abundant. *Phthalein 60 per cent.*

June 2. Dog has some diarrhoea; weight 21 lbs. *Phosphorous 5 mgs.* in oil subcutaneously.

June 10. Dog is in fair condition; weight 22 lbs. *Phosphorous 5 mgs.* in oil given subcutaneously.

June 18. Dog continues to have diarrhoea; weight 21½ lbs. 12 m., *phthalein 0.2 gm.* intravenously. 3 p. m., urine by catheter contains only faint traces of phthalein. Bile and albumin are absent.

June 19. Abundant feces. *Phthalein* 42 per cent.  
 June 20. Dog in fair condition; weight 20½ lbs. *Phosphorous* 5 mgs. in oil subcutaneously.  
 June 28. *Phosphorous* 5 mgs. in oil subcutaneously.  
 July 8. *Phosphorous* 5 mgs.; weight 19¼ lbs.  
 July 10. Condition fair; weight 19½ lbs. 10 a. m., *phthalein* 0.2 gm. intravenously. 2.30 p. m., urine *phthalein* ¼ per cent. 3 p. m., *phthalein* 0.  
 July 11. Abundant feces. *Phthalein* 4½ per cent.  
 July 24. Condition unchanged; weight 19 lbs. Sacrificed. Autopsy at once. All the organs are normal. Liver appears quite normal in gross. The bile passages show no abnormality. Microscopical section of liver is normal.

TABLE VI. Dog 12-105.—CHRONIC PHOSPHOROUS POISONING.

Date.	Phthal. in 24 hr.	Phthalein excreted.		Liver injury.	Weight.	Remarks.
		Feces.	Urine.			
Apr. 5	100	Percent.	Percent.		21½	Normal.
8	100	42	0		22	Do.
10	100	22	1.2	Phosph. 5 mg.	21	Dog is sick.
14	100	40	(7)	Phosph. 5 mg.	21	Hypersecretion (?).
15	100	15	Traces	Phosph. 5 mg.	21	Diarrhoea.
16	100	11		Phosph. 5 mg.	21	Blood in urine.
20	100	11		Phosph. 5 mg.	20½	
21	100	11		Phosph. 5 mg.	19½	
22	100	11		Phosph. 5 mg.	19	

## HYDRAZINE AND PHOSPHOROUS POISONING—EARLY CIRRHOSIS.

Dog 12-82.—Mongrel male; weight 17½ lbs.  
 April 5. 1 p. m., *phthalein* 0.1 gm. intravenously. *Hydrazine sulphate* 0.1 gm. subcutaneously. 7 p. m., urine by catheter contains abundant *phthalein*.  
 April 6. Feces abundant. *Phthalein* 20-22 per cent.  
 April 7. 0.2 gm. *hydrazine* subcutaneously.  
 April 8. Dog eats well; weight 16¼ lbs.

Plasma Lipase .10-10 Initial alkalinity.  
 .10-10 Butyric acidity.

.20-20 Acid production.

12 m., *phthalein* 0.1 gm. given intravenously. 5 p. m., urine contains *phthalein*, turning deep red with hydroxide.

April 9. Abundant feces. *Phthalein* 25-27 per cent. Dog does not appear intoxicated.

April 10. 3 p. m., weight 16½ lbs. *Phthalein* 0.1 gm. intravenously. 6 p. m., urine contains *phthalein*, 1½ per cent. 9 p. m., urine contains traces of *phthalein*.

April 11. Abundant feces. *Phthalein* 38-42 per cent.

April 14. Dog appears quite well. *Phosphorous* 5 mgs. in oil given subcutaneously.

April 15. Dog appears well; weight 17 lbs. *Phthalein* 0.1 gm. intravenously. 4 p. m., urine contains trace of *phthalein*.

April 16. Feces fairly abundant. *Phthalein* 33-35 per cent. Urine is negative for *phthalein*.

April 20. Dog is in a good condition; weight 17½ lbs. *Phosphorous* 7.5 mgs. in oil given subcutaneously.

April 21. Broth culture (0.3 cc.) 24 hour growth of *B. coli* given intravenously.

April 22. Dog appears in a good condition and eats food; weight 16¼ lbs. Blood plasma appears normal, and clot is firm.

Plasma Lipase .10-10 Initial alkalinity.  
 .60-70 Butyric acidity.

.70-80 Acid production.

12 m., *Phthalein* 0.1 gm. intravenously. 5 p. m., urine contains *phthalein*, ¼ per cent, and no bile.

April 23. Abundant feces. *Phthalein* 25-32 per cent.

April 24. *Phosphorous* 7.5 mgs. in oil given subcutaneously.

April 25. 11 a. m., *phthalein* 0.1 gm. intravenously; weight 15 lbs. 4 p. m., urine contains abundant *phthalein* 1 per cent, and bile pigments are present.

April 26. Abundant feces. *Phthalein* 30 per cent.

April 27. Dog found dead. Autopsy: Bilateral pleurisy with about 1 to 200 cc. of turbid exudate. The mediastinal tissues everywhere are oedematous. The lungs are clear. Other viscera are negative except the liver. The liver lobules are slightly conspicuous and the color suggests some fatty change. Microscopical section: Liver shows evidence of beginning cirrhosis. The connective tissue about the portal spaces is oedematous and contains numbers of wandering cells. There are clumps and strands of new formed fibroblasts, and in places indefinite buds suggesting the structures assumed to grow from the bile ducts or strands of liver cells. Phagocytes containing pigment debris are present in these areas. In some lobules polymorphonuclear leucocytes are quite numerous, suggesting a persistence of the infection produced by the injection of *B. coli*. The liver cell columns are somewhat distorted. The liver cells in general are pretty normal looking. Some of them contain small fat droplets, however, and the bile canaliculi as a rule are distended with yellow colloid material. There are no necroses. Wandering cells of the mononuclear type are pretty numerous everywhere. It is obvious that one is dealing here with a subacute infectious and toxic injury to the liver, bringing about progressive changes with proliferation of fixed tissue cells and definite suggestion of early cirrhosis. Death was due in great part to pleurisy and empyema with no evidence of grave liver insufficiency. It is probable that the colon bacillus, together with the phosphorous, were responsible.

TABLE VII. Dog 12-82.—HYDRAZINE AND PHOSPHOROUS POISONING.

Date.	Phthal. in given.	Phthalein excreted.		Liver injury.	Weight.	Remarks.
		Feces.	Urine.			
Apr. 5	100	Percent.	Percent.		Pounds.	
8	100	27	+	Hydrazine.	17½	
10	100	42	1	Do.	16½	
14	100	35	Traces.	Phosph. 5 mg.	17	
15	100	35	Traces.	Phosph. 7.5 mg.	17	
16	100	35	Traces.	Phosph. 7.5 mg.	17	
20	100	35	Traces.	Phosph. 7.5 mg.	17	
21	100	35	Traces.	Phosph. 7.5 mg.	17	
24	100	35	Traces.	Phosph. 7.5 mg.	16½	<i>B. coli</i> (0.3 cc. broth) intravenously.
25	100	35	Traces.	Phosph. 7.5 mg.	15	Lipase above normal.
27	Death	..	..	..	..	Bile in urine. Empyema—early cirrhosis.

The preceding experiment (Dog 12-82) shows the effect of hydrazine sulphate, which causes a drop in *phthalein* output, as in the case of other drugs which injure the liver. This drug causes a fatty change in the liver cell with little cell necrosis, and it is interesting that the lipase is normal at this time, although in fatal hydrazine poisoning the plasma lipase will be much increased. *Phosphorous* was then given, followed by a broth culture of *B. coli* to combine the action of the poison with an infection. Under certain conditions (Opie)<sup>3</sup> this will cause cirrhosis and such was found to be the case in this experiment, where autopsy showed connective tissue proliferation and some distortion of liver cell columns.



## ECK FISTULA AND CHLOROFORM POISONING.

Dog 12-51.—Brindle bull, female; weight 27 lbs.  
 April 3. 12 m., *phthalein* 0.2 gm. intravenously. 5 p. m., urine contains traces of *phthalein*.

April 4. 11 a. m., feces abundant. *Phthalein* 45 per cent.

April 24. Dog in excellent condition; weight 26½ lbs. Operation as usual for *Eck fistula*.

April 25-27. Dog is well and eats.

April 28. Wound scratched open, but was closed again by deep sutures. This necessitated slow granulation.

May 9. Dog in excellent condition; weight 26¼ lbs. 11 a. m., *phthalein* 0.2 gm. intravenously. 4 p. m., urine contains *phthalein* 1 per cent. 6 p. m., urine contains no *phthalein*.

May 10. Feces are abundant. *Phthalein* 45 per cent.

May 17. Dog in a good condition; weight 29 lbs. 5 p. m., *phthalein* 0.2 gm. intravenously.

May 18. Urine of previous night contains 1 per cent *phthalein*. Abundant feces during forenoon. *Phthalein* 43 per cent.

June 2. 3 p. m., dog in excellent condition; weight 29 lbs. *Chloroform anesthesia* 2 hours. The anæsthetic was poorly taken and a large amount of the drug given.

June 3. 12 m., dog is quiet, but does not look very sick. *Phthalein* 0.2 gm. intravenously. Blood plasma clots in normal time, but the clot is decidedly soft. Fibrinogen estimation 50 to 100 mgs.

Plasma Lipase .00-.10 Initial alkalinity.

1.30-.90 Butyric acidity.

1.30-1.00 Acid production.

5 p. m., urine by catheter contains bile and albumin. *Phthalein* 2½ per cent. Dog is bleeding from neck and the granulating abdominal wound, indicating a serious drop in fibrinogen content.

June 4. 10 a. m., dog found dead. Feces were abundant in the cage. *Phthalein* 5 to 10 per cent ± (color red and very difficult to read). Intestinal contents collected carefully. *Phthalein* 6 per cent. Gall bladder contains *phthalein* ½ per cent. Abdominal cavity contains about 200 cc. of bloody fluid, and there had been a good deal of bleeding externally as well as internally. Lungs showed numerous purple moist areas of bronchopneumonia. All the tissues showed icterus. Liver showed central necrosis. Microscopical section: The usual hyaline, central necrosis is present, involving about ¼ or more of every lobule. The liver cells about the portal spaces show fatty degeneration.

TABLE VIII. DOG 12-51—ECK FISTULA AND CHLOROFORM.

Date.	Phthal- ein given.	Phthalein excreted.		Liver injury.	Weight.	Remarks.
		Feces.	Urine.			
		Per cent.	Per cent.		Pounds.	
Apr. 3	.200	45	Traces.	....	27	Normal.
24	....	....	....	....	26½	Eck fistula produced.
May 9	.200	45	1	Eck Fistula.	26½	
17	.200	43	1	do.	29	
June 2	....	....	....	Chloroform 2 hrs.	29	Anæsthetic poorly taken.
3	.200	7	2½	....	29	Bleeding, fibrinogen low.
4 Death.	6 (intestine).	..	....	....	...	Lipase 5 times normal

## ECK FISTULA.

Dog. 12-2.—Black and tan mongrel, female.

Feb. 1. Ether anesthesia with operation as usual and production of the *Eck fistula*.

Feb. 2. Dog is recovering rapidly and drinks milk.

Feb. 3. Weight 13½ lbs.

April 1. 12 m., *phthalein* 0.1 gm. intravenously. Weight 15

lbs. 5 p. m., catheterised urine turns deep red on adding sodium hydroxide, showing considerable amount of *phthalein*.

April 2. 2 p. m., feces abundant. *Phthalein* 17 per cent.

April 8. 12 m., *phthalein* 0.1 gm. intravenously; weight 16 lbs. 4 p. m., urine contains *phthalein* ¼ per cent.

April 9. Abundant feces. *Phthalein* 20 per cent.

April 15. *Phthalein* 0.2 gm. intravenously; weight 15½ lbs.

4 p. m., urine by catheter *phthalein*, 2 per cent.

April 16. 9 a. m., urine from cage contains *phthalein* in traces. 10 a. m., abundant fluid feces. *Phthalein* 30 per cent.

May 26. Dog in excellent condition and there has been steady improvement in general condition; weight 17 lbs. 11 a. m., *phthalein* 0.1 gm. intravenously. 5 p. m., urine contains 0.1 per cent.

May 27. 2 p. m., abundant fluid feces. *Phthalein* 36 per cent.

May 30. 5 p. m., *phthalein* 0.1 gm. by stomach tube.

May 31. Night urine from cage contains no *phthalein*. Following the purge abundant feces were collected. *Phthalein* 45 per cent.

June 2. 11 a. m., *phthalein* 0.1 gm. by stomach tube, after a period of fasting for 24 hours, insuring practically an empty stomach.

June 3. 10 a. m., abundant fluid feces. *Phthalein* 58 per cent.

June 17. 10 a. m., *phthalein* 0.1 gr. intravenously; weight 17 lbs. 12 m., urine contains *phthalein*, 0.3 per cent. 4 p. m., urine contains *phthalein*, 0.1 per cent ±.

June 18. 10 a. m., abundant feces. *Phthalein* 40-41 per cent.

June 19. Abundant feces. *Phthalein* present only in faint traces.

June 21. Plasma Lipase .10-10 Initial alkalinity.

.30-30 Butyric acidity.

.40-40 Acid production.

July 10. 10 a. m., dog appears well. 16¼ lbs. *Phthalein* 0.1 gm. intravenously. 2.30 p. m., urine, *phthalein*, 0.4 per cent.

3 p. m., urine by catheter. *Phthalein* 0.5 per cent. Purged.

July 11. Abundant feces. *Phthalein* 38-40 per cent.

TABLE IX. DOG 12-2.—ECK FISTULA.

Date.	Phthal- ein given.	Phthalein excreted.		Liver injury.	Weight.	Remarks.
		Feces.	Urine.			
		Per cent.	Per cent.		Pounds.	
Feb. 1	....	....	....	....	15	Eck fistula produced.
Apr. 1	.100	17	1	Eck Fistula	15	
8	.100	20	1	....do	16	
15	.200	30	2	....do	15½	
May 26	.100	26	0.1	....do	17	
June 2	.100*	38	0	....do	18	*Given <i>phthalein</i> by stomach.
17	.100	40	0.4	....do	17	
July 10	.100	40	0.9	....do	16	Dog well.

This experiment (Dog 12-2) shows how an *Eck fistula* dog may give a low *phthalein* output some weeks after the operation. These dogs often die during the first month with signs of obscure intoxication and perhaps suffer from hepatic insufficiency. This dog was in a rather poor condition for 2-3 weeks after the operation and then gradually and steadily improved in general health. It will be noted that the *phthalein* curve shows a steady rise in output. *Phthalein* is found in the urine in all *Eck fistula* dogs and we believe this indicates a certain type of liver injury; note also the increase in lipase. The preceding experiment (Dog 12-51) shows no difference in *phthalein* output before and after the *Eck fistula*, but it should be noted that the dog was in perfect condition and

gained weight after the operation. Fatal chloroform poisoning and Eck fistula showed the same reaction in every respect, as noted in preceding experiments (Chloroform).

#### RECOVERY AFTER ONE YEAR'S DURATION.

Dog 61.—Adult mongrel, female; weight 13 lbs.

May 25, 1912. Ether anaesthesia and an operation as usual. *Eck fistula* produced. Dog made a good recovery and has appeared normal during the past year.

April 5, 1913. Dog is normal and active; weight 13½ lbs. 1 p. m., *phthalein* 0.1 gm. intravenously. 7 p. m., urine contains *phthalein* 0.3 per cent.

April 6. Abundant feces. *Phthalein* 44 to 45 per cent. Urine contains faint traces of *phthalein*.

June 18. Dog in excellent condition; weight 15 lbs. 12 m., *phthalein* 0.1 gm. intravenously. 3 p. m., urine by catheter contains 0.8 per cent.

June 19. Abundant feces. *Phthalein* 42 per cent.

June 20. Soft feces. *Phthalein* 6 per cent. *Phthalein* total 48 per cent.

Plasma Lipase	.10-10 Initial alkalinity.
	.20-15 Butyric acidity.
	.30-25 Acid production.

#### PASSIVE CONGESTION, ASCITES AND CHLOROFORM INJURY.

Dog 12-44.—Irish terrier, female; weight 13 lbs.

Jan. 21. Ether anaesthesia and operation (McClure). The vena cava between the diaphragm and heart was exposed and its lumen narrowed to an extreme degree by placing fine silk sutures going through and through the vein wall. The caliber of the vein at the end of the operation was estimated between 1 and 2 mm., the original diameter being about 8 mm.

Jan. 22-23. Dog recovering well from operation.

Jan. 27. Abdomen is somewhat swollen.

Jan. 31. There is well-marked oedema of the legs and abdominal wall; weight 19½ lbs. Respiration is grunting and labored. 3 p. m., *phthalein* 0.1 gm. intravenously. 5 p. m., ascitic fluid 1000 cc. removed. *Phthalein* was absent.

Feb. 1. 3 p. m., 1500 cc. ascitic fluid removed. *Phthalein* not demonstrable in 500 cc.

Feb. 3. Subcutaneous oedema is diminishing; weight 18½ lbs. Collateral venous circulation is conspicuous over the abdomen.

Feb. 4. Weight 20 lbs., and dyspnoea is well marked, due to the pressure of the ascitic fluid. 1400 cc. pale, straw-colored fluid removed from abdomen.

Feb. 6. Weight 17 lbs. The subcutaneous oedema is clearing. The venous collaterals are very conspicuous. Ascitic fluid, 600 cc. removed.

Feb. 7. Weight 18 lbs. Ascitic fluid 1700 cc. removed.

Feb. 15. Weight 17 lbs. Dog has excellent appetite and appears in perfectly good health. Ascitic fluid 600 cc. removed.

Feb. 18. Abdomen is very tense; weight 19½ lbs. Ascitic fluid 1500 cc. removed.

Feb. 20. 1000 cc. ascitic fluid removed.

Feb. 28. Weight 18½ lbs. Ascitic fluid 1800 cc. removed.

March 11. Ascitic fluid 900 cc. removed.

March 28. Ascitic fluid 1500 cc. removed. Weight after removal 14½ lbs.

March 31. Weight 20½ lbs. Ascitic fluid 2000 cc. removed. The oedema has reappeared over the abdomen, which is very tense.

April 1. 1 p. m., *phthalein* 0.1 gm. intravenously; weight 16½ lbs. 2.30 p. m., urine contains no *phthalein*.

April 2. Abundant fluid feces. *Phthalein* 32 per cent.

April 7. Ascitic fluid 2000 cc. removed.

April 12. Weight 21 lbs. Abdomen and hindlegs very oedematous. 12 m., *phthalein* 0.1 gm. intravenously. 3 p. m., urine contains no *phthalein*.

April 13. 12 m., feces abundant. *Phthalein* 39-41 per cent. Dog is quite dyspnoeic, due to accumulation of fluid; weight 22½ lbs. Ascitic fluid 2000 cc. removed.

April 15. Ascitic fluid 2000 cc. removed.

April 22. Ascitic fluid 1000 cc. removed.

April 24. 600 cc. ascitic fluid removed. Spleen after removal of fluid is large, nodular and easily palpable. Liver can be palpated.

May 9. Weight 19½ lbs. Dog is in excellent condition; no subcutaneous oedema. Collaterals are very conspicuous over the abdomen. 11 a. m., *phthalein* 0.1 gm. intravenously.

May 10. Feces abundant. *Phthalein* 53 per cent.

May 13. Ascitic fluid 1000 cc. removed.

May 20. Abdomen is greatly swollen; weight 22½ lbs. Ascitic fluid 3000 cc. removed. 3 p. m., chloroform anaesthesia for two hours.

May 21. 11 a. m., *phthalein* 0.1 gm. intravenously; weight 16 lbs. 12.30 p. m., urine contains *phthalein*, 0.1 per cent. 2.30 p. m., urine contains abundant *phthalein*, 2 per cent. 3 p. m., ascitic fluid 500 cc. removed. After centrifuging a clear amber fluid is obtained, which turns to a clear rose red on the addition of sodium hydroxide. It is obvious that the *phthalein* after chloroform poisoning has passed into the ascitic fluid, as well as into the urine. The ascitic fluid

Ascitic fluid Lipase	.10-10 Initial alkalinity.
	.30-30 Butyric acidity.
	.40-40 Acid production.

5 p. m., urine contains *phthalein*, 1 per cent. 9 p. m., urine contains *phthalein*, 1 per cent.

May 22. Abundant fluid feces. *Phthalein* 19 per cent.

May 23. 9 a. m., abundant feces. *Phthalein* 0. Urine contains *phthalein* ½ per cent and bile tests are positive. Dog is hungry and eats pretty well. 5 p. m., urine contains no *phthalein* but plenty of bile pigments.

May 24. Urine contains traces of bile pigments. Dog appears quite normal. During this time there has been no accumulation of ascitic fluid.

May 26. Dog is active and hungry; weight 14½ lbs. 11 a. m., *Phthalein* 0.1 gm. intravenously. 5 p. m., urine contains traces of *phthalein*.

May 27. Abundant feces. *Phthalein* 30 per cent.

May 28. Feces contain no *phthalein*.

June 9. Ascites beginning to reappear; weight 15½ lbs. Collateral veins over abdomen are inconspicuous.

June 16. Weight 18 lbs. Dog is in a good condition.

June 17. 11 a. m., *phthalein* 0.1 gm. intravenously; weight 18 lbs. 2.30 p. m., urine contains only the faintest trace of *phthalein*. 3.30 p. m., ascitic fluid 800 cc. removed. Centrifuging gives a clear amber colored fluid which undergoes no change on the addition of sodium hydroxide showing the absence of any *phthalein*.

Ascitic fluid Lipase	.10-05 Initial alkalinity.
	.05-10 Butyric acidity.
	.15-10 Acid production.

After removal of fluid, spleen is not as hard and easily palpable and liver cannot be felt.

June 18. No feces; and purgatives are vomited.

June 19. Abundant feces soiled with vomitus. *Phthalein* 23 per cent. It is possible that, due to the delay in purgation, there

had been some absorption of phthalein, but it is evident that the output is definitely diminished.

July 10. Dog well; good appetite. Ascitic fluid accumulates slowly and collaterals are conspicuous; weight 17½ lbs. 10 a. m., *Phthalein* 0.1 gm. intravenously. 2.30 p. m., urine contains mere trace of phthalein.

July 11. Abundant fluid feces. *Phthalein* 43 per cent.

July 21. Dog in good condition; 17 lbs. Sacrificed. Autopsy at once. The peritoneal cavity contains about 1700 cc. of ascitic fluid. The peritoneal cavity shows a little thickening of the serous coverings. The liver lobules are glued together by this same chronic inflammatory reaction undoubtedly associated with repeated tapplings. Liver is enlarged, but has diminished in size considerably with the escape of blood. The gall bladder and bile ducts are quite normal. Bile escapes easily into the duodenum. On section the liver lobules have rather conspicuous centers, many of which contain blood. The spleen is but little increased in size. The other organs are normal. Kidneys show definite congestion of the cortex. The pleural cavity shows no adhesions except between the vena cava and the lung where the

sutures are placed. The lumen of the vena cava measures 7-8 mm. in circumference when opened and is covered by a smooth, intimal lining. The sutures are embedded in the wall, causing little pouchlike bulgings just below the constriction. The vein below is slightly thickened.

Microscopical section: The liver is characteristic of passive congestion. There is central atrophy and fatty degeneration. Some of the lobules show almost complete disappearance of the parenchyma and here the walls of the sinusoids are thickened. There is a slight increase in connective tissue about many of the portal structures. The liver parenchyma as a rule about the margin of the lobule is quite normal.

The preceding experiment is of considerable interest. Experimental passive congestion of the tissues and organs below the diaphragm can be easily produced by this method devised by R. D. McClure. It will be noted that the ascites did not appear at once and almost a week was required for advanced accumulation of ascitic fluid. The dog presented all the common signs of passive congestion of the abdominal viscera. In spite of this engorgement of the liver its functional capacity was but little impaired and the phthalein excretion rose as the collateral circulation became established and the liver adjusted itself to the changed conditions. This is in harmony with the observations of phthalein excretion in human cases.

Chloroform anesthesia for two hours caused the usual sharp drop in phthalein output and, most interesting of all, the appearance of phthalein in the urine and ascitic fluid. Phthalein did not occur in the urine and ascites without acute liver injury. It is clear from this and other experiments that the presence of injured liver cells in the body modifies the phenol-tetrachlorophthalein so that it can pass the kidney filter. It is obvious from this experiment that the phthalein is modified so that it can pass through the endothelial filter elsewhere than in the kidney and appears in the ascitic fluid. Lipase of the plasma is greatly increased during liver injury and the lipase of the ascitic fluid is about double normal during chloroform poisoning. The repair of the chloroform liver injury which advances so rapidly in normal dogs is found to be greatly delayed, probably due to the impaired circulation. Autopsy showed characteristic passive congestion of the liver with some central atrophy and connective tissue reaction.

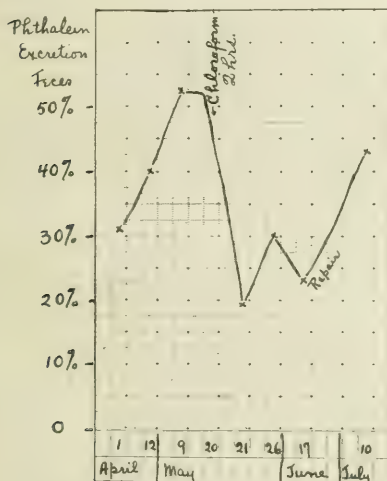


CHART III. Dog 12-44.—Passive Congestion and Chloroform Poisoning.

TABLE X. Dog 12-44.—PASSIVE CONGESTION AND CHLOROFORM.

Date.	Phthal- ein given.	Phthalein excreted.			Liver injury.	Weight.	Remarks.
		Feces.	Urine.	Ascites.			
		Per cent.	Per cent.	Per cent.		Pounds.	
Jan. 21	....	....	....	....	....	13	Vena cava partial- ly occluded above diaphragm.
31	....	....	....	....	C. P. C.	19½	Oedema of abdomen.
31	.100	..	0	0	....	....	Ascitic fluid re- moved.
Apr. 1	.100	32	0	..	C. P. C.	16½	Ascitic fluid re- moved (500 cc.).
12	.100	40	0	..	....	21	Oedema of legs.
May 9	.100	53	..	..	....	19½	
21	....	....	....	....	Chloroform 2 hrs.	20½	Ascitic fluid 900 cc. in ascites.
21	.100	19	4½	+	....	16	
26	.100	39	Trace.	..	....	14½	
Jun. 17	.100	28	Trace.	0	....	18	
Jul. 10	.100	43	Faint trace.	..	....	17½	

#### HEMATOGENOUS ICTERUS AND ETHER ANESTHESIA.

Dog 12-1.—Fox terrier, female; weight 14½ lbs.

April 22. 12 m., dog is normal. *Phthalein* 0.1 gm. intravenously. 5 p. m., urine contains no phthalein.

April 23. Feces rather abundant. *Phthalein* 38 per cent.

April 25. *Phthalein* 0.1 gm. given by stomach tube.

April 26. Feces abundant. *Phthalein* 60 per cent.

June 3. 11 a. m., ether anesthesia for 45 minutes. At the end of this time *phthalein* 0.1 gm. given intravenously. 5 p. m., catheterized urine contains no phthalein.

June 4. No feces; and dog vomits purgatives.

June 5. Feces are abundant. *Phthalein* 30 per cent. It is probable that this slight decrease below normal can be explained by the delay in purgation, which renders the amount extracted rather uncertain, because of possible absorption.

June 17. 12.30 p. m., dog is quite well; weight 15½ lbs. Intra-



venous injection of *hemoglobin solution* from normal dog. Normal washed red blood cells (85 cc.) were laked with 100 cc. distilled water and given intravenously. 2.30 p. m., dog vomits profusely and appears somewhat intoxicated. 3.30 p. m., second intravenous injection of *hemoglobin solution* exactly as at 12.30, the same amount being used. This was followed by an injection of *phthalein 0.1 gm.*, followed by 100 cc. of 0.9 per cent salt solution. Urine obtained at this time by catheter was a deep blood red color. Bile pigments positive (Huppert's test).

June 18. 10 a. m., urine was soiled with vomitus and feces, and showed traces only of phthalein. Soft feces and vomitus collected, *phthalein 30 per cent.* 11 a. m., urine (catheterized) contains hemoglobin and bile with considerable albumin. Phthalein negative.

June 19. Abundant feces. Phthalein 10 per cent. Total phthalein 40 per cent.

July 26. Dog in good condition; weight 16 lbs. Sacrificed and autopsy at once. Thorax and heart are normal. Lungs show grayish nodules of organizing pneumonia (parasites). Liver appears normal in every way in gross. Bile can be easily squeezed through the bile papilla into the duodenum and the bile passages and gall bladder are quite normal. Microscopical section shows no abnormality. Other viscera normal.

The preceding history demonstrates two points: First, the administration of ether anesthesia does not cause the appearance of phthalein in the urine as is the case with chloroform anesthesia, where we know a definite liver necrosis is effected. This period of anesthesia covers the time usually employed in the various operations upon the liver and gives control of this factor. Second, the intravenous injection of a solution of hemoglobin which leads to hematogenous icterus and heaping up of bile in the liver canaliculi, does not influence the output of phthalein. The liver is able to carry this extra load without giving any signs of impaired efficiency, as far as excretion of this drug is concerned.

#### ANEMIA AND HEMATOGENOUS ICTERUS.

Dog 12-58.—Small fox terrier, female; weight 14½ lbs.

April 18. 2 p. m., *phthalein 0.1 gm.* intravenously. 5 p. m., urine contains no phthalein.

April 19. Feces are abundant. *Phthalein 35-40 per cent.*

May 12. Dog is normal; weight 16 lbs. Phenylhydrazine (1 per cent solution) 4 cc. given subcutaneously.

May 13. Phenylhydrazine 5 cc. subcutaneously. Hemoglobin (Sahli) 90-95 per cent.

May 14. Urine is high colored. Bile pigments negative. Phenylhydrazine 10 cc. subcutaneously.

May 15. Phenylhydrazine 10 cc. subcutaneously. Urine is high colored, but negative for bile pigments.

May 16. Phenylhydrazine 10 cc. subcutaneously. Urine contains traces of bile.

May 17. Urine contains large amounts of bile and is very dark. Dog appears rather sick; weight 14 lbs. 5 p. m., *phthalein 0.1 gm.* intravenously.

May 18. Dog shows slight icterus tint in skin. Urine of night contains very faint traces of phthalein. Hemoglobin 44 per cent. No feces.

May 19. 10 a. m., abundant feces but the extraction was very difficult and accurate reading was impossible. *Phthalein 30 per cent ±.*

May 20. Bile present in urine. Dog appears rather sick.

May 22. Dog is improving; hemoglobin 46 per cent; weight 13 lbs. 12 m., *phthalein 0.1 gm.* intravenously. 5 p. m., urine contains traces of phthalein.

May 23. Abundant feces. *Phthalein 35 to 41 per cent.*

May 24. 10 a. m., more feces. Phthalein 2 per cent.

May 28. Dog appears normal. Hemoglobin 67 per cent. Phenylhydrazine (1 per cent solution) 10 cc. subcutaneously.

May 29 to June 4. Phenylhydrazine 10 cc. subcutaneously given each day.

June 5. Hemoglobin 27 per cent. Urine is free from bile. and very high colored; weight 14½ lbs. 12 m., *phthalein 0.1 gm.* intravenously. 3.30 p. m., urine contains no bile and a definite trace of phthalein. Phenylhydrazine given subcutaneously.

June 6. Abundant feces. *Phthalein 40 per cent.*

June 8. Phenylhydrazine 10 cc. given subcutaneously; weight 13½ lbs.

June 9. Dog is active; weight 13½ lbs. Hemoglobin 25 per cent. 12.30 p. m., *phthalein 0.1 gm.* intravenously. 4 p. m., urine contains traces of phthalein and gives positive tests for bile pigments.

June 10. Abundant fluid feces. *Phthalein 55 per cent.* Urine contains bile pigments.

TABLE XI. DOG 12-58.—ANEMIA AND ICTERUS.

Date.	Phthalein given.	Phthalein excreted:		Liver injury.	Hemoglobin.	Weight.	Remarks.
		Feces.	Urine.				
		Per cent.	Per cent.		Per cent.	Pounds.	
Apr. 18	.100	10	0	....	95	14½	Normal.
May 12	....	0	0	....	95	16	Phenylhydrazine daily May 12-16. Bile in urine.
17	.100	..	Faint trace.	Icterus.	44	14	
19	....	39	do.	....	..	..	Delay in purgation. Bile traces in urine.
22	.100	43	Trace.	....	46	13	Phenylhydrazine daily May 28 to June 8.
28	....	..	..	....	67	14	Bile in urine.
Jun. 5	.100	40	..	Anemia.	27	14½	
9	.100	55	Trace.	Icterus.	25	13½	Bile in urine.

#### ANEMIA AND HEMATOGENOUS ICTERUS.

Dog 12-129.—Brindle bull dog, female; weight 28½ lbs.

May 28. Hemoglobin (Sahli) 98 per cent. 5 p. m., *phthalein 0.2 gm.* intravenously.

May 29. Urine contains faint traces of phthalein. 3 p. m., abundant feces. *Phthalein 45 per cent.*

May 29-30. Phenylhydrazine (10 cc. of a 1 per cent solution) subcutaneously.

June 2. Phenylhydrazine 15 cc. subcutaneously.

June 3. Hemoglobin 60 per cent. Phenylhydrazine (15 cc.) subcutaneously.

June 4. Phenylhydrazine (15 cc.) subcutaneously; weight 24½ lbs.

June 5. Hemoglobin 40 per cent. 15 cc. phenylhydrazine subcutaneously. 12 m., *phthalein 0.2 gm.* intravenously; weight 24 lbs.

June 6. Abundant feces. *Phthalein 41 per cent.*

June 8. Dog is rather weak and pale; weight 22 lbs. Phenylhydrazine 15 cc. subcutaneously.

June 9. Dog is very pale. Hemoglobin 15 per cent. Blood taken directly from vein and read in four volumes. 12 m., *phthalein 0.2 gm.* intravenously. 4 p. m., urine contains bile pigments. No albumin. *Phthalein 0.1 per cent ±.*

June 10. Night urine contains traces of phthalein and considerable bile pigments. Abundant fluid feces. *Phthalein 39 per cent.*

June 16. Dog has lost a great deal of weight and is not eating well. Hemoglobin 50 per cent; weight 17½ lbs.

June 17. 11 a. m., *phthalein 0.2 gm.* intravenously. 4 p. m., urine contains faint traces of phthalein.

- June 18. Abundant feces. Phthalein 36-38 per cent.  
 June 19. More feces. Phthalein 10 per cent.  
 June 23. Dog is improving; weight 19½ lbs.

TABLE XII. DOG 12-129.—ANEMIA AND ICTERUS.

Date.	Phthal- ein given.	Phthalein excreted.		Liver injury.	Hemo- globin.	Weight.	Remarks.
		Feces.	Urine.				
		Per ct.	Per ct.		Per ct.	Pounds.	
May 28	.200	45	Traces.	.....	98	28½	Normal.
Jun. 3	....	..	..	Anemia.	60	24½	Phenylhydrazine daily May 29 to June 8.
5	.200	41	..	.....	40	24	
6	.200	..	9.1 ±	Icterus.	15	..	Bile plus in urine.
10	..	30	..	do.	..	..	Dog pale and weak.
17	.200	..	..	.....	50	17½	Emaciation.
18	..	37	..	.....	..	..	Delay in excret'n.
19	....	10 ±	..	.....	..	..	Dog improving.

The two preceding experiments (Dogs 12-58 and 12-129) were performed to throw some light on the question of hematogenous icterus and liver function. In these two experiments the blood was destroyed in vivo by means of phenylhydrazine given daily. The destruction must have been considerable, as the hemoglobin dropped from 98 per cent to 15 per cent and icterus was evident, with bile pigments abundantly present in the urine; yet the phthalein output in the feces remained at a normal level. A very slight fall in the second case could not have been recognized without an accurate normal base line, and we may assume that hematogenous icterus of a considerable degree does not impair liver function, as expressed by phthalein excretion.

The question of anemia may be considered at this point, and it may be concluded that a secondary anemia of moderate severity will not influence liver activity.

## OBSTRUCTIVE ICTERUS.

- Dog 12-138.—Young brindle bull, female; weight 24½ lbs.  
 June 9. 12 m., phthalein 0.2 gm. intravenously. 4.30 p. m., urine contains very faint traces of phthalein.  
 June 10. Abundant fluid feces. Phthalein 4½ per cent.  
 June 16. Ether anesthesia and operation with ligation of common bile duct.  
 June 17. Dog is in a good condition. Urine contains much bile pigment. 10 a. m., phthalein 0.2 gm. intravenously; weight 21½ lbs. 12 m., urine by catheter contains bile pigments and phthalein 4½ per cent.  
 June 18. Night urine contains phthalein ½ per cent ±. Icterus is evident in the sclerae. The dog is lively and hungry.  
 June 19. Condition the same. Night urine contains phthalein 1 per cent ±. Bile is very abundant.  
 June 20. Soft clay feces. Phthalein 0. Urine contains much bile, no albumin and definite traces of phthalein. 12 m., urine by catheter contains no phthalein. Icterus seems to be less intense. Phthalein 0.2 gm. intravenously.  
 June 21. Night urine contains considerable phthalein. 9.30 a. m., fresh urine contains phthalein 0.8 per cent. 10 a. m., urine by catheter contains bile and phthalein 0.3 per cent. 11 a. m., soft pasty feces contain traces of phthalein and obviously the duct is cutting through and establishing the outflow from the liver.  
 June 22. Feces abundant. Phthalein 12 per cent. 12 m., urine by catheter contains only faint traces of bile and no phthalein. Icterus has disappeared.

- June 23. Dog is hungry and appears normal; weight 22½ lbs. Urine by catheter is free from bile and shows a faint cloud of albumin. Feces contain phthalein 2-5 per cent. 12.30 p. m., phthalein 0.2 gm. intravenously. 3 p. m., urine contains phthalein 0.4 per cent. 4 p. m., urine contains only traces of phthalein.

- June 24. Abundant feces. Phthalein 60-62 per cent.  
 June 25. Urine and feces contain no phthalein.  
 July 22. 10 a. m., dog normal; weight 22½ lbs. Phthalein 0.2 gm. intravenously. 5.00 p. m., urine by catheter. Phthalein present in traces. Bile pigments absent.  
 July 23. Abundant fluid feces. Phthalein 39 per cent.

TABLE XIII. DOG 12-138.—OBSTRUCTIVE ICTERUS.

Date.	Phthal- ein given.	Phthalein excreted.		Liver injury.	Weight.	Remarks.
		Feces.	Urine.			
		Per ct.	Per ct.		Pounds.	
June 9	.200	34	0	.....	24½	Normal.
16	..	..	..	Icterus	24½	Bile duct ligated.
17	.200	..	4½	.....	21½	Bile + + in urine.
18	..	..	..	.....	21½	Jaundice of sclerae.
19	..	..	1 ±	..	20	..
20	.200	0	0	..	20	Jaundice less intense.
21	..	Traces.	1	..	20	Bile duct cut through.
22	..	13	0	..	22½	..
23	.200	4 ±	0.4	..	22½	Bile 0 in urine.
24	..	60	0	..	..	..
25	..	0	0	..	..	Dog normal.
July 22	.200	39	Traces.	.....	22½	..

The preceding experiment (Dog 12-138), as well as the following one (Dog 12-90), gives clear evidence that acute obstructive icterus caused by closing the common bile duct is associated with actual injury of the liver parenchyma. Other tests of liver function support this view. It will be seen that the phthalein escapes in the urine in obstructive icterus, but not in hematogenous icterus to any extent. This experiment shows very nicely how simple ligation of the common bile duct will cause obstruction for only about five days. The ligature cuts through and lies in the duct wall, but the ducts above may remain dilated and scar tissue formation may cause partial stricture (see below Dog 12-90). The abnormally high phthalein output following the last injection indicates a patent duct and probably a sweeping out of stagnant bile containing some phthalein of the previous injection.

## OBSTRUCTIVE ICTERUS AND PHENYLHYDRAZINE POISONING.

- Dog 12-90.—Small mongrel, male; weight 11 lbs.  
 April 6. Ether anesthesia. Operation and ligation of common bile duct.  
 April 7-9. Bile is present in the urine.  
 April 10. Dog seems normal. There is no icterus and bile duct is probably cutting through. 3 p. m., phthalein 0.1 gm. intravenously; weight 11 lbs. 9 p. m., urine contains phthalein 0.3 per cent.  
 April 11. Urine contains faint traces of phthalein. Feces are abundant and fluid. Phthalein 43 per cent.  
 April 14. Phenylhydrazine sulphate 0.1 gm. given subcutaneously.  
 April 15. Dog appears rather sick; weight 10 lbs. 1 p. m., phthalein 0.1 gm. intravenously. Phenylhydrazine 0.1 gm. given subcutaneously. 5 p. m., urine soiled with a little vomitus. Phthalein 1½ per cent.  
 April 16. No feces. Urine plus vomitus phthalein, 4 per cent. 4 p. m., small amount of feces. Phthalein present in traces, 1 to 2 per cent ±.

April 17. Jaundice is evident in skin. Dog is quite dull. One soft stool. Phthalein present in mere traces.

April 18. Dog is somewhat better; weight  $8\frac{1}{2}$  lbs. Urine is rich in bile pigments and contains a trace of albumin. 2 p. m., phthalein 0.1 gm. intravenously. 4 p. m., urine contains traces of phthalein and much bile pigment.

April 19. Urine contains abundant phthalein, 2 per cent. One fluid stool. Phthalein 8 per cent.

April 22. Urine contains no bile and no albumin. Dog is much better; weight 9 lbs. 12 m., Phthalein 0.1 gm. intravenously. 5 p. m., urine contains phthalein, 2 per cent.

April 23. Abundant feces. Phthalein 35 per cent.

May 12. Dog is in good condition and weighs 11 $\frac{1}{2}$  lbs. Sacrificed. Autopsy at once. Organs are normal except liver and bile passages. There are old adhesions around the bile duct between the duodenum and liver at the site of operation. Bile and hepatic ducts are dilated to about double normal size with definite stricture at the site of ligatures on the common duct. These ligatures have cut through and are situated in the wall of the duct, a part of the ligatures protruding into the lumen of the duct, which is narrowed at this place. The ligatures are crusted with salts and occlude the lumen in part, but a part of the obstruction is due to the narrowing effected by the new-formed scar tissue. The liver is practically normal in gross. Microscopical section shows practically normal parenchyma except for an occasional fat droplet in a liver cell. The portal tissues in places show a little increase in stroma and wandering cells. It is possible that with this narrowed duct the phenylhydrazine poisoning by the production of inspissated bile may have caused temporary complete obstruction, and that the great drop in output may have been due to this instead of profound liver injury.

TABLE XIV. Dog 12-60.—OBSTRUCTIVE ICHEMUS AND PHENYLHYDRAZINE POISONING.

Date.	Phthalein excreted.		Liver injury.	Weight.	Remarks.
	Feces.	Urine.			
Apr. 7-9	.....	.....	Icterus	11	Bile duct ligated.
10	1.100	45	.....	11	Bile + catheter cut through.
14	.....	.....	Phenylhydrazine 0.1 gm.	10	Dog moribund.
15	1.100	.....	.....	10	Dog moribund.
16	.....	.....	.....	10	Bile ++ in urine
17	.....	.....	.....	8 $\frac{1}{2}$	Icterus
18	1.100	.....	Traces.	8 $\frac{1}{2}$	Icterus
19	.....	8	.....	9	Dog is moribund.
20	.....	.....	.....	9	Bile 0 in urine.
21	.....	.....	.....	9	Moderate amount of bile in urine.
May 12	.....	.....	.....	11 $\frac{1}{2}$	Sacrificed.

The autopsy findings in the preceding case (Dog 12-90) are of especial interest and suggest transient periods of complete obstruction associated with a narrowed common duct and inspissated bile due to liver injury (phenylhydrazine). The last injection of phthalein gave interesting information. The dog had no bile in the urine and seemed normal, yet the phthalein of the feces was below normal and the urine contained 2 per cent. This of itself spoke for liver injury and impairment which was shown by the autopsy.

#### ALEURONAT IN PORTAL VEIN.

Dog 12-77.—Fox terrier, male; weight 15 lbs.

April 18. 2 p. m., phthalein 0.1 gm. intravenously. 5 p. m., urine contains no phthalein.

April 19. Abundant feces. Phthalein 39 per cent.

May 21. Dog in perfect condition; weight 16 $\frac{1}{4}$  lbs. Ether anaesthesia and operation with injection into portal vein of a 1 per cent suspension of aleuronat, made up with starch solution and sterilized. 5 cc. of this solution injected slowly in portal vein.

May 22. 12 m., phthalein 0.1 gm. intravenously. Dog looks quite ill. 6 p. m., urine contains phthalein,  $\frac{1}{2}$  per cent  $\pm$ .

May 23. Feces are abundant. Phthalein 41-45 per cent. Urine contains no albumin, no phthalein, but small amounts of bile pigments.

May 24. 10 a. m., urine contains no albumin, and no bile pigments. Intravenous injection  $\frac{1}{2}$  cc. of 24-hour broth culture of *B. coli*.

May 28. Dog is active as usual; weight 16 lbs. 5 p. m., phthalein 0.1 gm. intravenously.

May 29. Urine contains no phthalein. Feces abundant. Phthalein 45 per cent.

June 4. Dog sacrificed in another experiment. Liver is practically normal in gross. Microscopical sections give no positive evidence of changes in the neighborhood of the portal structures, but it is very likely that repair following this relatively trivial injury would go on with such rapidity as to restore structures completely to normal within a period of two weeks.

#### LIVER INJURY BY CAUTERY.

Dog 12-60.—White bull-dog, female; weight 22 lbs.

April 1. 1 p. m., dog is quite normal. Phthalein 0.2 gm. intravenously. 4 p. m., urine is very abundant and contains faint traces of phthalein.

April 2. 2 p. m., abundant feces. Phthalein 50-55 per cent.

June 4. Dog is in excellent condition; weight 23 $\frac{1}{4}$  lbs. Ether anaesthesia with laparotomy and exposure of liver. Three lobes of the liver were cauterized deeply, using a large iron cautery. The necrosis was fairly extensive. After the operation, given  $\frac{1}{4}$  grain of morphia.

June 5. 12 m., dog appears in good condition. Phthalein 0.2 gm. intravenously. 3 p. m., urine by catheter contains phthalein, 0.5 per cent. 5 p. m., urine contains phthalein, 0.1-0.2 per cent.

June 6. Abundant fluid feces. Phthalein 33-35 per cent.

June 7. 12 m., dog in good condition; weight 23 $\frac{1}{4}$  lbs. Phthalein 0.2 gm. intravenously. 2.30 p. m., urine contains much phthalein, 1-2 per cent. Bile pigments are present. 8.30 p. m., urine contains phthalein, 1-2 per cent  $\pm$ .

June 8. 11 a. m., urine by catheter contains no phthalein, and small amounts of bile pigments. No feces obtained.

June 9. 10 a. m., abundant fluid feces. Phthalein 40 per cent. 3 p. m., more feces. Phthalein 0.

June 10. 4 p. m., dog appears normal; weight 22 $\frac{1}{2}$  lbs. Phthalein 0.2 gm. intravenously.

June 11. No feces obtained.

June 12. Abundant fluid feces. Phthalein 48-52 per cent.

TABLE XV. Dog 12-60.—LIVER CAUTERY.

Date.	Phthalein given.	Phthalein excreted.		Liver injury.	Weight.	Remarks.
		Feces.	Urine.			
Apr. 1	.200	Per cent. 55	Per cent. 55	.....	22	Normal.
June 4	.....	.....	.....	Cautery	.....	Deep cauterization of three lobes.
5	.200	35	0.6	.....	23 $\frac{1}{4}$	.....
7	.200	40	2 $\pm$	.....	23 $\frac{1}{4}$	Bile in urine.
10	.200	52	.....	.....	22 $\frac{1}{2}$	Dog well.



## LIVER INJURY BY CAUTERY.

Dog 12-137.—Small fox terrier, female; weight 13 lbs.

June 2, 12 m., ether anaesthesia and operation. Liver lobes burnt with actual cautery, three lobes being seared deeply. At the end of the operation *phthalein* 0.15 gm. intravenously. 5 p. m., urine contained traces of *phthalein*.

June 3. No feces.

June 4. Feces abundant. *Phthalein* 15 per cent. 12 m., *phthalein* 0.1 gm. intravenously; weight 11½ lbs. 3 p. m., urine by catheter contained definite amounts of *phthalein*, giving a cherry-red solution on adding hydroxide. 5 p. m., urine by catheter contained *phthalein*.

June 5. Abundant feces. *Phthalein* 48 per cent.

June 6. Blood stained feces with some vomitus. *Phthalein* 10 per cent.

June 25. Dog sacrificed. Heart, lungs, spleen and kidney and intestinal tract normal. Dense adhesions about the liver, particularly over the areas which were cauterized. There is a definite cavity containing thick, shreddy, digested material, together with bits of necrotic liver parenchyma, whose wall is made up of dense granulation tissue measuring 3 or 4 mm. in thickness. This occupies a portion of one liver lobe. In places there has been marked constriction with distortion of the neighboring parenchyma. The liver lobules in general outside of the area of injury are normal, except for some central fatty degeneration. Microscopical section shows the wall of granulation tissue made out in gross. The liver lobules in association with this tissue are somewhat distorted, but the portal tissue is not markedly thickened. The lobules in general show a moderate grade of central fatty degeneration and leucocytes are fairly numerous in the capillaries. This change is more marked close to the liver scars. It is evident that a considerable amount of liver parenchyma had been destroyed by this procedure and replaced in part by inflammatory tissue, in which can be seen embedded the hyaline masses of necrotic parenchyma. A slight grade of bacterial infection is probably superposed, indicated by a considerable number of polymorphonuclear leucocytes. In places the dead liver tissue acts as a foreign body, causing the formation of syncytial masses of giant cells.

The three preceding experiments (Dogs 12-77, 60 and 137) illustrate a type of direct liver injury which is not due to any drug or poison capable of influencing the condition of other organs; for example, the kidneys. The injection of aleuronat into the portal vein will cause liver necrosis and we may imagine this process to have taken place in the first experiment. The *phthalein* output in the feces was not influenced by this minor liver injury, but *phthalein* appears in the urine, and it is impossible to attribute this to any kidney injury or to any process except actual liver injury.

Actual cauterization of the liver gives a massive destruction of liver parenchyma, such as might result in amebic abscess of the liver or extensive metastatic involvement in tumor growth. This procedure gives a definite fall in *phthalein* output in the feces and *phthalein* appears in the urine as a result of parenchyma injury.

## PHTHALEIN IN URINE DEPENDENT UPON LIVER INJURY.

Dog 12-117.—Mongrel male, adult; weight 17½ lbs.

May 16. 3 p. m., chloroform anaesthesia 2 hours.

May 17. 9 a. m., urine contains bile pigments. *Phthalein* 0.2 gm. intravenously. 10 a. m., urine, 30 cc., contains faint traces of *phthalein*. 10.30 a. m., urine, 50 cc., contains *phthalein* 0.3

per cent. 11 a. m., urine, 10 cc., contains *phthalein*, 0.4 per cent. 11.30 a. m., dog was transfused directly into Dog 12-118. Then perfused with normal salt solution and these washings after removal of red blood cells and defibrination given also to Dog 12-118. These washings contain 2 mgs. of *phthalein* estimated from a fraction of the material.

Autopsy performed at once. All the tissue gave a bright red reaction with sodium hydroxide, indicating large amounts of *phthalein*. The contents of the intestine, washed out carefully, are rich in bile, but contain not a trace of *phthalein*, indicating a delay in excretion. Bile in gall bladder contained no *phthalein*. The mucosa of the gall bladder after washing gave a very deep pink color with sodium hydroxide, showing the presence of *phthalein* in the blood vessels of the mucosa. Liver shows little change in gross except conspicuous lobulations and increase in size. Under the microscope early liver necrosis is quite obvious, involving about three-fourths of every liver lobule. The liver was removed and ground up with sand with the formation of a uniform emulsion. To this was added a solution containing 200 mgs. of *phthalein*, and normal salt was added sufficient to make a fairly uniform paste. This mixture was allowed to stand in a water bath at 38° to 40° C. for three hours, used in Dog 12-119.

Dog 12-118.—Mongrel, male; weight 14 lbs. Ether anaesthesia and bleeding from femoral artery (225 cc.). Immediately after this bleeding direct transfusion from Dog 12-117 was done, using femoral artery to femoral vein. After the transfusion 300 cc. of the serum washings (Dog 12-117) were given intravenously by gravity. 12.25 p. m., urine by catheter. *Phthalein* 0. 4.20 p. m., urine by catheter. *Phthalein* positive. Definite rose red color on adding sodium hydroxide. 6 p. m., urine contains faint traces of *phthalein*.

May 18. Feces abundant. *Phthalein* 0. This dog received only a few milligrams of *phthalein* by means of this transfusion, as shown by the feces, which contain no demonstrable *phthalein*, yet the *phthalein* had been so changed as to escape through the kidney filter.

Dog 12-119.—Active fox terrier, female; weight 13¼ lbs. Intravenous injection of liver emulsion from Dog 12-117. The ground up liver mash plus 0.2 gm. *phthalein* incubated at 38-40° C. for three hours was made faintly alkaline with sodium hydroxide and squeezed through a cloth, centrifuged and filtered through cotton. 145 cc. of this thick, viscid filtrate given intravenously very slowly. The *phthalein* contained in this amount equaled .029 gm. 4 p. m., intravenous injection started. 5 p. m., injection completed. 4.45 p. m., urine by catheter contained hemoglobin, which was removed by boiling and filtering. The clear amber filtrate on the addition of hydroxide showed a definite *phthalein* red color. Dog died during the night. Autopsy showed little of interest. The intestinal contents contained a few milligrams of *phthalein*, which could not be read accurately.

Dog 12-133.—Mongrel, female; weight 13½ lbs.

May 29. 3 p. m., chloroform anaesthesia 2 hours.

May 30. 10 a. m., *phthalein* 0.2 gm. intravenously. 11 a. m., Ether anaesthesia and bleeding from femoral. Blood defibrinated and clear amber serum obtained by centrifugalization. The dog was perfused with 1 litre of 0.9 salt. The washings collected and treated as the whole blood. First fraction yielded 200 cc. of clear amber serum, second fraction (washings) yielded 500 cc. pale serum. Both fractions given intravenously in Dog 12-134. Autopsy performed at once (Dog 12-133). Organs are normal except the liver, which shows an early necrosis involving about one-half of each liver lobule. Urine in bladder contains *phthalein*, 1 per cent.

Dog 12-134.—Fox terrier, female; weight 12 lbs.

May 30. 1 p. m., intravenous injection of blood serum obtained from Dog 12-133. This blood-phthalein mixture had circulated in contact with injured liver tissue for one hour. 2.15 p. m., urine in a clean cage contained traces of albumin. 2.45 p. m., urine by catheter 30 cc. Phthalein definite rose red with sodium hydroxide.

May 31. Feces collected. Phthalein 3 per cent indicating that the amount of phthalein introduced intravenously in this dog did not exceed 20 milligrams and probably not much over 10 milligrams.

The preceding group of experiments (Dogs 12-117 and 12-133) give the final proof that injured liver cells modify the phthalein in the blood stream so that the drug appears in the urine in appreciable amounts, which does not occur with a normal liver. Circulation of phthalein for one hour in contact with an injured liver (chloroform) is followed by the appearance of phthalein in this dog's urine, but most important of all this blood phthalein mixture when given to a normal dog intravenously is followed by the appearance of phthalein in the normal dog's urine. This rules out any secondary effect of the liver poison upon the kidney.

#### DISCUSSION.

The normal output of phenoltetrachlorphthalein in the feces of dogs is remarkably constant. From a study of the tables above it will be found that the normal feces output rarely falls below 40 per cent and rarely exceeds 50 per cent—the usual normal being about 45 per cent. It will be seen that the individual normal variation is even less, and by careful work it is easy to fix the normal base line of any given dog with considerable accuracy. This enables one to make careful study of small fluctuations in phthalein output and this will be of interest in many forms of experimental work with hepatic function.

The drop in phthalein output appears to run parallel to the amount of parenchyma injury. Following a short chloroform anaesthesia or the injection of small doses of hydrazine or phosphorous there is a small drop in phthalein output, while after a grave injury or one sufficient to cause death the phthalein curve falls to zero. The mechanism of liver repair is familiar (Whipple and Sperry)<sup>4</sup> and with this repair the phthalein output returns to normal. In some instances following liver repair the output may rise above normal (Dog 12-53), as has been reported in earlier work with blood fibrinogen (Whipple and Hurwitz).<sup>5</sup> This may speak for a period of hyperactivity of these newly formed liver cells. After a trifling injury to the liver (*e. g.*, a small dose of phosphorous) there may be a period of *hypersecretion* of phthalein, and we may imagine the drug acting as an irritant to the secreting parenchyma—a stage perhaps preceding that of actual cell injury or necrosis.

Passive congestion, when of moderate degree, will cause little impairment of function and show a normal output, but during periods of marked circulatory embarrassment the liver will not be able to function properly and the output drops. The Eck fistula liver may present a normal output or show

considerable impairment and this variation will parallel the general condition of the animal. The explanation of this variation in dogs with Eck fistulae is not clear, in that we do not understand the causation of the liver degeneration which is usually present in such animals dying with symptoms of intoxication. It is well to bear in mind how much change in the hepatic circulation can be effected without impairing the dog's health or influencing the phthalein curve.

Destruction of the liver parenchyma by the actual cautery will cause a prompt drop in phthalein output, and it is probable that the presence of this injured tissue and the inflammatory reaction more than the actual loss of parenchyma is responsible for the drop in the curve. This experiment simulates in a way the human cases of amebic abscess or even metastatic tumor growth in the liver, which are associated with considerable parenchyma destruction.

Delay in phthalein excretion can be demonstrated following acute liver injury, but can be of little value in work with the feces. In experiments where the dogs are sacrificed a few hours after chloroform injury and phthalein injection, it will be found that the bile is free from phthalein or contains but traces, whereas it is known that normally the drug appears in the bile within fifteen to thirty minutes.

The urine contains no phthalein or at most a trace (faint rose red with alkali) following injection of the amounts of phthalein employed in normal dogs. After acute liver injury of any type (chloroform, phosphorous, aleuronat, cautery) the urine collected in the first six hours will contain 0.2 to 8.0 per cent. It seems that the injured liver cells modify the phthalein so that it can pass the kidney filter; moreover, so that it can escape into the ascitic fluid of a dog with passive congestion. This is not due to any kidney injury, as would be indicated by the liver cautery experiments, but is proved conclusively by the transfusion of blood containing phthalein from a dog with liver injury into a normal animal. In spite of the minimal amount of phthalein received by the normal dog, the urine shows its escape through the kidney.

Obstructive icterus of any considerable degree makes this test of little value. It will give some evidence of the amount of acute liver injury which may be present, depending upon the amount of the drug escaping in the urine. Some of the drug will be stored in the bile, but the greater part will be changed to some non recognizable form which cannot be recovered from the body. Hematogenous icterus and anemia of considerable severity do not modify phthalein excretion by the liver.

Chronic liver injury will offer more difficulties of interpretation, for we cannot expect to diagnose liver scars by means of any test unless the scars are of sufficient size and number to impair its functional activity. A cirrhotic liver like a diseased heart may have periods of normal activity, when it is quite capable of carrying on its normal work. The reserve force of an organ is always considerable and after an injury has healed, even perhaps leaving considerable scar tissue, the parenchyma may be able to function properly and sufficiently

for the bodily needs. Under such circumstances one cannot demand too much from any functional test, as the drug excretion may be normal, even though the liver be working close to its limit capacity and be liable to a period of broken compensation at any moment. There is a great need of accumulated data bearing on these points, careful clinical and anatomical study of cases with various types of liver lesion. Attention should not be limited to one test, but all forms of liver tests should be employed and compared with the clinical and anatomical findings.

This test promises much in the study of derangements of the hepatic parenchyma, physiological and anatomical. Its great value is that it may give some *quantitative values* con-

cerning liver injury, and for this reason, with accumulated experience, may be of value to the clinician. It surely will be of considerable value in various experimental studies concerned with liver function and impairment. We hope to report further work along these lines in the near future.

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<sup>3</sup> Opie, E. L.: J. Exp. Med., 1910, XII, 367.

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## A TEST FOR HEPATIC INJURY: BLOOD LIPASE.

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Work with this ferment lipase was first started in this laboratory in connection with a study of acute hemorrhagic pancreatitis. It was hoped that the ferment might appear in the urine after experimental pancreatitis and be of diagnostic value. Hewlett<sup>1</sup> had noted the appearance of this ferment in the urine of animals with acute pancreatitis, and Opie<sup>2</sup> had recorded its presence in a human case. It was thought that the fat necroses which are so constant in this disease were produced by this ferment and that it might escape in the urine under these conditions.

A routine study of dogs' urine convinced us that small amounts of lipase (.05 to .20 cc.) were present at times normally. It was also found that after acute pancreatitis had been produced by the injection of bile into the duct or otherwise, lipase did appear in the urine promptly. The lipase content sometimes rose as high as 0.50-.60 cc. in the first hour after the operation, with a rapid fall to .10 cc. or even zero in six hours. Small amounts of lipase sometimes persisted in the urine for a day or so after the operation, but this seemed to bear no relation to the extent of pancreatic injury.

It was soon found that lipase appeared in the urine whether the pancreas was injured or not, and it became apparent that the anaesthesia was the sole cause for the sudden appearance of this ferment in the urine. Ether or chloroform will cause its appearance in the urine, but it is to be kept in mind that ether causes no rise in blood lipase, as it causes no liver necrosis. Chloroform, as is noted below, causes a marked and prompt rise in blood lipase associated with liver injury. The blood and urine lipase are in no way parallel, as lipase appears in the urine, especially during the first six hours after anaesthesia, while the plasma lipase reaches its maximum in 6-12 hours and remains high for two days or longer. We are familiar with the reports of other workers who have studied the lipase in the blood, but they have come to no very definite conclusions. Some workers claim that lipase is absent from

blood serum, but they are in the minority.\* Bauer<sup>3</sup> describes small fluctuations in serum lipase in cases of tuberculosis, cancer and syphilis, but gives no careful anatomical study. Von Hess<sup>4</sup> finds the serum lipase to be uninfluenced by pancreatic extirpation, peritonitis, hyperthyroidism, thyroidectomy and ether anaesthesia. Serum lipase is not activated by bile salts.

In the experiments tabulated below very little detail is noted, but the lipase content is recorded in some of the experiments reported in full in a preceding communication (Whipple, Peightal and Clark).<sup>5</sup>

## METHOD.

The method (Loevenhart) for determining lipase in any of the body fluids may be outlined as follows: Four tubes are prepared, each containing 1 cc. plasma, serum, etc., diluted with 4 cc. distilled water and 0.3 cc. toluol added. To two of the tubes is added .26 cc. ethyl butyrate, the other two serving as controls. The tubes are all corked, shaken and incubated at 38° C. for 18 to 24 hours. They are cooled in ice water, three drops of azolitmin added as an indicator and titrated in pairs to a neutral reaction, using 1-10 normal acid and alkali. The two control tubes give the serum alkalinity to this indicator as about 0.1 cc. 1-10 normal acid. The butyrate tubes give the amount of acid production above the neutral point, and the sum represents the total acid production or lipolytic activity. This represents the amount of butyric acid which has been set free by the ferment, and it is estimated always in term of 1-10 normal acid. This may be spoken of as the blood lipase, serum or plasma, as the case may be.

It will be found that there is little difference between the plasma and serum lipase, the latter being a little higher because of the dilution of the plasma by the oxalate. The blood obtained from the dogs was almost always removed from a vein during life. Many of the specimens of human blood were obtained during life

\* A general presentation of the work done upon the ferment lipase will be found in the Handbuch der Biochemie, Oppenheimer, 1909.



and often shortly after death before the blood had clotted. Blood from the autopsy cases was usually drawn directly into oxalate by a trocar in the heart.

TABLE I.—LIVER NECROSIS IN DOGS—CHLOROFORM ANÆSTHESIA

No.	Acid production.	Alk. linity.	Basic acidity.	Period following liver injury.	Remarks.
C-9	.35-.35	.10-.10	.25-.25	Normal.	
C-9	.45-.50	.10-.10	.35-.40	30 minutes.	Chloroform 2 hrs.
C-9	1.70-1.50	0-.0	1.70-1.50	14 hrs.	Do.
89	.30-.35	.10-.15	.20-.20		Pregnant.
89	.35-.40	.10-.10	.25-.30	End of anæsthesia.	Chloroform 2 hrs.
88	.30-.25	.10-.10	.20-.15		Normal.
88	.35-.35	.10-.10	.25-.25	End of anæsthesia.	Chloroform 2 hrs.
88	.80-.85	.10-.10	.70-.75	3 hrs.	Do.
88	.55-.60	.10-.10	.80-.90	5 hrs.	Do.
C-19	.35-.40	.05-.10	.30-.30		Normal.
C-19	.42-.49	.10-.10	.32-.30	End of anæsthesia.	Chloroform 2 hrs.
C-19	1.60-1.40	.10-.10	1.50-1.30	5 hrs.	Do.
C-19	1.50-1.55	.10-.10	1.40-1.45	24 hrs.	Do.
C-19	1.45-1.45	.10-.10	1.35-1.35	2 days.	Do.
C-19	1.05-1.05	.15-.10	.90-.95	4 days.	Do.
C-9	.30	.05	.25		Normal.
C-9	.60-.65	.10-.10	.50-.55	2 hrs.	Chloroform 2 hrs.
C-9	1.65-1.80	.15-.10	1.50-1.70	2 days.	Do.
B-13	1.50-1.80	.10-.10	1.40-1.70	2 days.	Chloroform 2 hrs.
B-13	.35-.40	.10-.15	.25-.25	8 days.	Do.
12-48	1.10-1.40	.10-.10	1.00-1.30	2 days.	Chloroform 1 hr.
12-48	.70-.60	.10-.10	.60-.50	24 hrs.	Chloroform 2 hrs.
12-58	1.00-1.40	.10-.10	1.00-1.35	24 hrs.	Do.
12-141	.55-.80	.15-.15	.40-.65	4 days.	Bit of liver removed on 24 day. Shows hyaline necrosis.
12-141	.40-.50	.10-.10	.30-.40	5 days.	
11-141	.30-.30	.10-.10	.20-.20	6 days.	

\*Repair complete.

Table I gives a sufficient number of observations to show the plasma lipase reaction following a chloroform anæsthesia, which is known to produce a uniform central hyaline liver necrosis involving from two-fifths to three-fifths of each liver lobule. The lipase content rises rapidly after the end of anæsthesia, reaching a maximum in six to twelve hours and remaining pretty constant and uniformly elevated until the end of forty-eight hours, when a fall begins and returns to normal on the sixth day or a little later. This parallels the process of repair which goes on so rapidly in the liver during the week following chloroform injury. It will be seen that a shorter narcosis will cause a smaller rise in lipase (see Dog 12-48) when the experiments are done upon the same animal to exclude any individual variations. It is of importance that the individual variations are but slight. We may conclude that in general a high lipase indicates considerable liver necrosis and lesser amounts of necrosis will be associated with minor rises in plasma lipase. It is probable that some other factors may influence this reaction, and these will be discussed later.

Chart I shows in a diagrammatic way the combined observations of Table I. When the chloroform poisoning is fatal, leading to death on the third or sixth day, the lipase curve usually remains high as on the second day, but it may fall somewhat as in phosphorous poisoning. (See Chart III.)

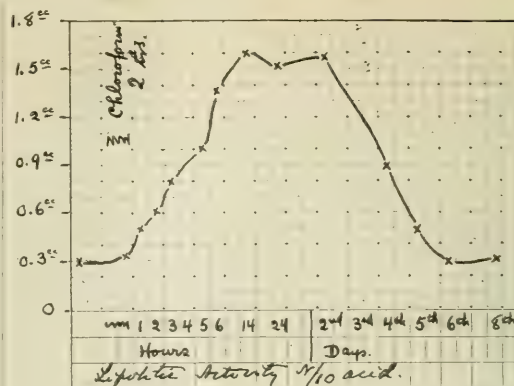


CHART I.—PLASMA LIPASE CURVE, LIVER INJURY, CHLOROFORM.

TABLE II.—PHOSPHOROUS AND HYDRAZINE POISONING IN DOGS.

No.	Acid production.	Alk. linity.	Basic acidity.	Period following liver injury.	Remarks.
12-88	1.55-1.20	.10-.10	1.45-1.10	24 hrs.	Phosphorous subcutaneous.
12-88	.70-.60	.10-.10	.60-.50	3 days.	Phosphorous subcutaneous.
12-88	.75-.70	.10-.10	.65-.60	6 days.	Phosphorous liver necrosis and fat.
12-82	.70-.80	.10-.10	.60-.70	2 days.	Phosphorous: death 7th day.
12-80	.85-.75	.10-.10	.75-.65	6 days.	Phosphorous liver.
12-82	.20-.20	.10-.10	.10-.10	2-3 days.	Hydrazine sulphate, 2 small doses.
12-87	.65-.65	.10-.10	.55-.55	2 days.	Hydrazine sulphate, lethal dose. Peripheral liver necrosis and fat.

TABLE III.—EEK FISTULA IN DOGS.

No.	Acid production.	Alk. linity.	Basic acidity.	Period following liver injury.	Remarks.
12-2	.40-.40	.10-.10	.30-.30	5 months.	Eek fistula.
61	.30-.25	.10-.10	.20-.15	13 months.	Do.
12-51	1.40-.90	.10-.10	1.30-.80	24 hrs.	Eek fistula plus chloroform 2 hrs. 1/2 liver lobule hyaline necrosis.
C-89	.40-.35	.10-.10	.30-.25		Slight icterus.
C-89	1.70-1.60	.05-.10	1.65-1.50	6 1/2 hrs.	Eek fistula plus hepatic artery ligation.
C-95	.20-.25	.10-.10	.10-.15		Normal.
C-95	1.60-1.65	.10-.10	1.50-1.55	5 1/2 hrs.	Eek fistula plus hepatic artery ligation.

Table II shows the lipase reaction following phosphorous and hydrazine poisoning. After phosphorous has been given in oil subcutaneously the maximum rise of the lipase curve is found after twenty-four hours, when it closely parallels the chloroform curve. On the following days, even in fatal cases,

the lipase falls to about one-half its highest level, but still remains well above normal until death. It is well known that in chloroform poisoning the amount of cell necrosis is very much greater than in phosphorous poisoning. The former poison attacks the nuclei of the liver cells, causing hyaline necrosis, and the latter injures the protoplasm, causing much fatty degeneration, but scattered liver cells show hyaline necrosis. This difference in amount of actual cell necrosis may explain some of the points of difference in the lipase curves.

Table III shows the plasma lipase of dogs with Eck fistulae of various duration. Shortly after operation an Eck fistula dog may show a very high plasma lipase and such dogs may show advanced liver degeneration, but rarely actual necrosis. When the fistula has been present for many months the lipase tends to return to normal, but may still show periods of elevation. The reaction to chloroform poisoning is identical with that of a normal dog. When an Eck fistula has been performed and the hepatic artery, with all its branches, ligated the dog will always die in 5-7 hours with characteristic symptoms. Under such conditions a very little blood can trickle through the liver by means of collaterals, but not sufficient to keep the cells alive, and they show evidences of autolysis at the end of the experiment. This small stream of blood which bathes these dying liver cells returns to the general circulation and is responsible for the great rise in plasma lipase found at the end of such experiments. Here, as elsewhere, the rise of blood lipase is associated with dead or injured liver cells in contact with the blood stream. In this instance the liver cells have been killed not by any poison, but by lack of blood.

TABLE IV.—OBSTRUCTIVE ICTERUS AND ACUTE HEMORRHAGIC PANCREATITIS IN DOGS.

No.	Acid production.	Alkalinity.	Butyric acidity.	Period following liver injury.	Remarks.
C-3	.45-.55	.10-.10	.35-.45	7 days.....	Bile duct ligated.
86	.30-.35	0-.05	.30-.30	5 days.....	Bile duct ligation; rupture & peritonitis.
B-42	.40-.35	.05-.05	.35-.30	14 days.....	Do.
B-3	1.20-.95	.10-.10	1.10-.85	8 days.....	Bile duct ligated; cholangitis; hyaline liver necroses.
S-4	.30-.35	.10-.10	.20-.25	24 hrs.....	Closed duodenal loop.
S-12	.25-.20	.10-.10	.15-.10	48 hrs.....	Closed duodenal loop; intoxication; corresponds to acute intestinal obstruction.
B-1	.20-.20	.10-.10	.10-.10	2 days.....	Acute hemorrhagic pancreatitis.
B-5	.30-.30	.10-.10	.20-.20	2 days.....	Acute hemorrhagic pancreatitis.

Table IV indicates the small rise in lipase which is associated with acute obstructive jaundice. Even when the bile duct ruptures with escape of bile into the peritoneal cavity with developing secondary peritonitis, the lipase shows but little rise above normal. However, if there is a *cholangitis*, with

hyaline necroses and liver injury, the lipase shows a great rise above normal, very much as in chloroform liver necrosis.

Acute hemorrhagic pancreatitis with profound injury and necrosis of the parenchyma shows a normal plasma lipase. As reported in a recent article on Hemorrhagic Pancreatitis (Whipple and Goodpasture)<sup>7</sup> the peritoneal exudate contains the same amount of lipase as does the plasma, except in the last stages of a fatal case, where it may be assumed that the processes of exudation and neutralization are at a standstill.

Closed duodenal loops in dogs cause acute intoxication and death, which is identical with or very similar to the intoxication and death of acute intestinal obstruction. Under such circumstances the lipase of the blood is quite normal.

TABLE V.—ECLAMPSIA AND TOXEMIAS OF PREGNANCY.

No.	Acid production.	Alkalinity.	Butyric acidity.	Autopsy liver.	Clinical diagnosis.	Remarks.
3672....	1.85-1.60	.10-.10	1.75-1.50	Massive portal necroses.	Eclampsia	Serum
3672....	1.80-1.70	.10-.10	1.70-1.60	do	do	Plasma
3883....	.85-1.15	.10-.15	.75-1.00	do	do	March 3, convulsions.
3883....	1.10-1.40	.10-.10	1.00-1.30	Massive portal necroses.	do	March 1, death.
3748....	.45-.50	.05-.05	.40-.45	Portal necroses.	do	Death 8 hrs. after first convulsion.
3963....	.25-.25	.10-.10	.15-.15	do	do	July 1, convulsions.
3963....	.20-.15	.10-.05	.10-.10	Very few portal necroses.	do	July 16, death.
5442....	1.30-1.25	.20-.20	1.10-1.05	do	do	Antepartum. Recovery 16th day.
5465....	.60-.50	.10-.10	.50-.40	do	do	Antepartum. Recovery 21st day.
5477....	.20-.20	.07-.05	.43-.15	do	do	Antepartum. Recovery 2d day.
5224....	.50-.55	.10-.15	.40-.40	do	do	Postpartum.
5358....	.20-.20	.10-.10	.10-.10	do	do	Antepartum.
5312....	.30-.30	.10-.10	.30-.20	do	Preeclamptic toxæmia.	No convulsions. Recovery 2 weeks.
5895....	.30-.30	.10-.10	.20-.20	do	Eclampsia (?).	Convulsions, epilepsy.
5887....	.35-.35	.15-.25	.20-.20	do	Eclampsia (?).	Chronic nephritis, renal degeneration.
5981....	.30-.30	.10-.15	.20-.15	do	Eclampsia (?).	Chronic nephritis, renal diagnosis.
3677....	.25-.30	.10-.10	.15-.20	Fatty degeneration.	Toxæmia.	
3687....	.30-.30	.10-.10	.20-.20	Marked fatty degeneration.	Vomiting of pregnancy.	

Table V is of particular interest, as it deals with eclampsia and various toxæmias of pregnancy. It may be admitted that at present there is a certain degree of confusion in this group of interesting diseases. Eclampsia is variously defined, but we wish to limit the term to that particular intoxication usually associated with convulsions, which presents characteristic hemorrhagic portal liver necroses. If this point is insisted upon, the diagnosis can never be absolutely certain unless death supervenes and a complete autopsy reveals the characteristic lesions.

The first four cases in the table were clinically typical eclampsias and the first two showed a very high blood lipase associated with a marked grade of portal hyaline necrosis. The third case shows a definite rise in lipase above normal, and liver necrosis was less marked. The fourth case shows a normal lipase and autopsy showed only a very few small portal

necroses. These were found only after very careful search in gross and by making a large number of microscopical sections. The areas involved were all situated at the hilum of the liver close to the large vessels and would have been missed completely by the usual routine examination and sections.

The next five cases of clinical eclampsia are of interest. Three show lipase much above normal, especially the cases with grave intoxication and slow recovery, and we may safely assume that liver necrosis was present in all. One case of intrapartum eclampsia showed a normal lipase and made a complete recovery by the second day. The last case was complicated with chronic nephritis and there may be some doubt about the diagnosis, as the lipase was normal.

Several cases of suspected eclampsia showed normal lipase and turned out to be chronic nephritis and even epilepsy in one instance.

The toxæmias and vomiting of pregnancy show normal lipase and the liver changes are limited to central fatty degeneration without liver necrosis.

From this analysis it is clear that the toxæmias of pregnancy, which have very high lipase, always present liver necrosis, and if peripheral the diagnosis of eclampsia is inevitable. Certain cases of eclampsia which are associated with very small and widely scattered portal necroses may show a normal lipase. The test is of value in differentiating various types of intoxication in pregnancy from true eclampsia.

TABLE VI.—LIVER NECROSIS IN HUMAN CASES.

No.	Acid production.	Alkalinity.	Butyric acidity.	Autopsy liver.	Clinical diagnosis.	Remarks.
3003....	.30-.30	.10-.10	.20-.20	.....	Cancer. Liver metastases.	April 4.
3003....	.60-.60	.10-.10	.50-.50	.....	Cancer; central necrosis and fat. infarctuses.	April 9, death.
3009....	.80-.80	.10-.10	.70-.70	.....	Septicæmia. Nephritis. Chloroform poisoning.	Chloroform 1½ hrs. 4th day, previously.
3726....	1.00-1.20	.10-.10	.90-1.10	.....	.....	6th day, death.
3726....	1.00-1.15	.05-.05	.95-1.10	.....	Central necrosis.	.....
3320....	.15-.15	.30-.25	.....	Few central necroses.	Leukaemia.	.....
3680....	.30-.75	.10-.15	.70-.60	½ central necroses	.....	Very acute.
3702....	.30-.55	.10-.10	.40-.45	Focal infarctuses.	Lobar pneumonia.	.....
3724....	.85-.75	.05-.05	.80-.70	½ central necrosis.	Aplastic anemia.	Necrosis missed in routine study.
3688....	.35-.45	.10-.10	.45-.35	1/100 focal liver necrosis.	Acromegaly. Infection.	Liver very fatty.

Table VI presents a group of cases in which liver necrosis was found at autopsy or in the routine histological study of the liver. It will be seen that the blood lipase is always above normal and often three to five times normal. The highest reading is in a case of late chloroform poisoning with death on the sixth day, in which case the liver necrosis involved a great part of every lobule. The readings in this case are exactly like those in the chloroform poisoning in dogs (Table I).

Table VII shows that chronic liver disease or icterus may be associated with a normal or even subnormal lipase. When

TABLE VII.—LIVER CIRRHOSIS AND ICTERUS IN HUMAN CASES.

No.	Acid production.	Alkalinity.	Butyric acidity.	Autopsy liver.	Clinical diagnosis.	Remarks.
3616....	.15-.20	.05-.05	.10-.15	Hemochromatosis.	.....	Cirrhosis and hemorrhage.
3485....	.40-.45	.10-.10	.30-.35	Many focal necroses.	Cirrhosis.	Icterus.
3634....	.10-.12	.05-.05	.05-.07	Focal necroses.	..... do.....	.....
Neizer....	.20-.25	.10-.10	.10-.15	.....	..... do.....	No clinical symptoms.
B. V....	.15-.10	.10-.05	.05-.05	.....	..... do.....	Marked toxæmia and icterus.
3665....	.20-.20	.10-.10	.10-.10	Slight cirrhosis.	Chronic nephritis.	Passive congestion.
Jones....	.20-.20	.10-.10	.10-.10	.....	Icterus 18 mos.	Tumor head of pancreas.
White....	.20-.20	.10-.10	.10-.10	.....	Icterus 4 mos.	Operation. Cancer head of pancreas.
3754....	.25-.20	.05-.05	.20-.15	Cancer: liver necroses.	Cancer icterus	Liver necrosis. No cellular reaction.
Woods....	.15-.15	.10-.10	.05-.05	.....	Icterus 3 mos.	Gall stones.

liver necrosis is combined with either of the above we may expect to see a definite rise in lipase, but this is not invariable. It is probable that chronic disease of the liver affects in some way this reaction against necrosis and injury which in the normal liver so constantly brings about the over-production or escape of lipase. One case (3754) with long-standing icterus, presents rather extensive hyaline central necrosis and normal lipase. It is of interest that although the necrosis obviously had been present over twenty-four hours, there had not been the slightest cellular reaction nor cell digestion which in most cases proceeds with great speed.

TABLE VIII.—NEPHRITIS. BLOOD DISEASES AND DIABETES.

No.	Acid production.	Alkalinity.	Butyric acidity.	Autopsy liver.	Clinical diagnosis.	Remarks.
3700....	.15-.20	.10-.10	.15-.20	Slight fatty degeneration.	Acute nephritis.	.....
3907....	.10-.10	.10-.10	.00-.00	Slight fatty degeneration.	Nephritis.	Subacute endocarditis and nephritis.
3665....	.20-.20	.10-.10	.10-.10	Slight cirrhosis.	Chronic nephritis.	Passive congestion.
Schwab....	.25-.25	.15-.15	.10-.10	.....	.....	Hemorrhagic disease.
Shema....	.20-.25	.05-.10	.15-.15	.....	Chronic leukaemia.	Hemorrhagic disease.
3916....	.30-.30	.00-.00	.30-.30	Fatty degeneration.	Pernicious anemia.	Acute case.
3742....	.20-.20	.10-.10	.10-.10	Fatty degeneration.	Acute diabetes.	Child 1½ years.
3855....	.35	.15	.20	Slight fatty degeneration.	Diabetes.	.....

Tables VIII and IX show quite a number of diseases with normal blood lipase. It is of interest that diabetes with definite lipemia shows a normal lipase. Nephritis, acute and chronic, causes no fluctuation in the lipase. Various types of blood disease where we may assume considerable disintegration of blood cells and abnormal marrow activity, show normal blood lipase. All acute infections show a normal lipase except those where the intoxication has caused more or less liver necrosis, focal or diffuse.



TABLE IX.—INFECTIONS.

No.	Acid production.	Alkalinity.	Butyric acidity.	Autopsy liver.	Clinical diagnosis.	Remarks.
3479....	.20-.15	.10-.10	.10-.05	Parenchymatous.	Typhoid.	No liver necroses.
3705....	.20-.22	.10-.10	.10-.12	Slight fatty degeneration.	Lobar pneumonia.	Plasma.
3705....	.35-.30	.10-.10	.25-.20	Slight fatty degeneration.	do.	Serum.
Newton	.40-.35	.10-.10	.30-.25	do.	do.	Toxaemia severe.
3751....	.20-.25	.10-.10	.10-.15	Liver tuberculosis.	do.	Miliary tuberculosis.
3668....	.20-.20	.10-.10	.10-.10	Caseous liver tuberculosis.	do.	Pulmonary tuberculosis.
3686....	.20-.25	.10-.10	.10-.15	Normal.	do.	Sarcomatosis.
Aro....	.20-.20	.15-.15	.05-.05	Normal.	Normal.	70 years.

dogs. Blood lipase in normal persons or animals is remarkably constant. It may be stated with considerable certainty that liver necrosis, however produced, in a liver previously normal, causes a characteristic rise in blood lipase from 0.2 cc. to 1.2 cc. or even higher—a rise of five to eight times normal. This rise reaches its maximum after twelve to twenty-four hours and may remain at this level for twenty-four hours or longer in fatal cases. The curve of blood lipase then falls slowly to normal on the sixth or eighth day with repair of the injured parenchyma. Small liver injuries with necrosis cause less marked rise in lipase and more prompt return to normal. Very trivial liver injuries even with a little true hyaline necrosis may not give a recognizable rise in lipase. Poisons like chloroform which produce hyaline liver necrosis give a

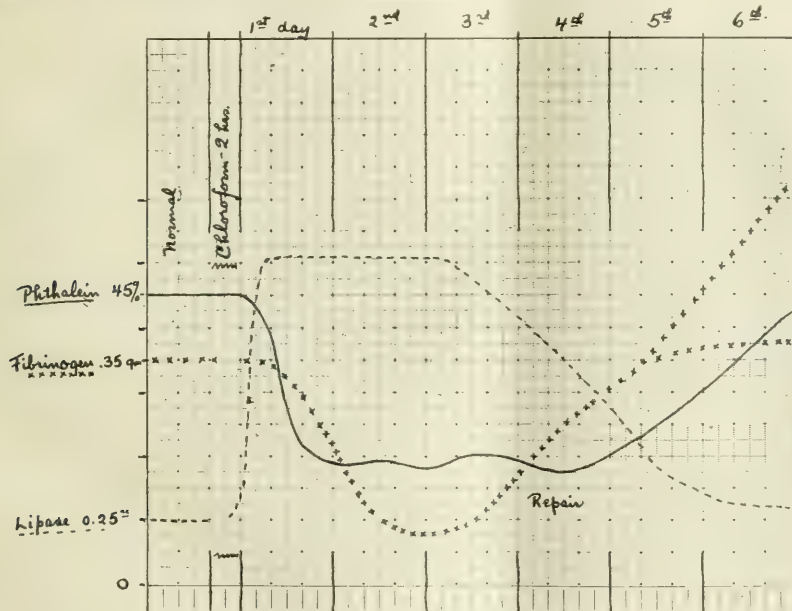


CHART II.

Chart II shows in a diagrammatic way the various changes in phthalein, fibrinogen and lipase which follow a chloroform anaesthesia. Anaesthesia for two hours will cause a central hyaline liver necrosis involving two-fifths to three-fifths of every liver lobule. During the process of repair there is a gradual return to normal and the fibrinogen curve may go far above normal (Whipple and Hurwitz).<sup>4</sup>

Chart III shows in the same way the reaction following a fatal liver injury by chloroform or phosphorous. Death may supervene on the third to the sixth day. The lipase curve may reach a considerably higher level and the fibrinogen content may fall to zero; the curves represent the average findings.

#### GENERAL DISCUSSION.

The preceding tabulated observations are quite uniform in the human cases as well as in the experiments performed on

higher and more prolonged rise in lipase than other poisons like phosphorous or hydrazine, which cause less true hyaline necrosis and much more fatty degeneration.

Liver necrosis which has been caused by acute intoxication or infection gives a lipase reaction identical with chloroform injury. The liver of fatal chloroform poisoning is very like that of acute yellow atrophy, and it is certain that in the latter instance the blood lipase will be found to be much above normal. The liver necroses associated with eclampsia, leukaemia, pneumonia, septicæmia, etc., all give a constant reaction in blood lipase, depending somewhat upon the extent of the necrosis.

From a study of Table VII it will be noted that this blood lipase reaction to liver injury may not be normal in chronic icterus or advanced cirrhosis. So, too, it will be found that at

times the normal sequence of autolysis of the dead hyaline cells and of inflammatory cellular reaction does not proceed under these conditions. Icterus of long standing may be associated with normal lipase, but at its onset may cause a slight rise above normal. Cholangitis which is associated with parenchyma injury will show a rise of lipase far above normal (Table IV).

Profound changes in blood supply of the liver (Eck fistula, or Eck fistula with hepatic artery ligation) will bring about cell degeneration or even cell death in the latter case and cause a corresponding rise in blood lipase.

pected eclampsia showed normal lipase and subsequently proved to be chronic nephritis, vomiting of pregnancy with fatty liver, epilepsy, etc.

Finally, it may be stated that a study of the lipase of the blood will show a definite rise above normal in practically all cases of eclampsia, liver injury with necrosis due to poisons, intoxications or infections, acute yellow atrophy, cholangitis and abscess of liver with considerable destruction of liver tissue. Cirrhosis of the liver may show a subnormal lipase; it may react to liver injury by a rise in blood lipase, but this point will require more study.

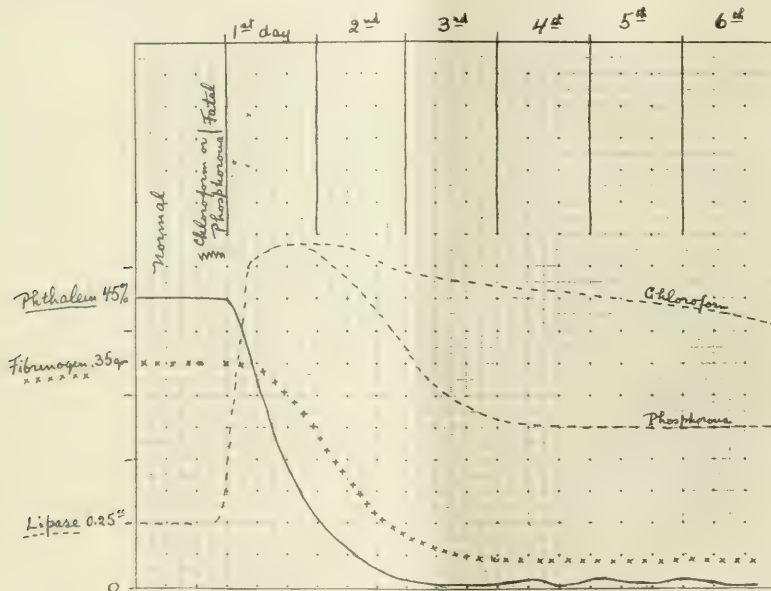


CHART III.

A great variety of acute intoxications not associated with liver injury show no fluctuations in plasma lipase. In this group we may include acute hemorrhagic pancreatitis, acute intestinal obstruction, acute or chronic nephritis with uremia, leukæmia, pernicious anaemia, diabetes, etc.

Difficulties of diagnosis between true eclampsia and the various toxæmias of pregnancy are common and this test will be of great help, provided the name eclampsia is limited to that type of intoxication associated with portal hyaline liver necroses. One case of true eclampsia (Table V) showed a normal lipase and at autopsy it required the most careful search to reveal a very few small but typical portal hyaline necroses. The very small amount of injured liver tissue was not sufficient to modify the blood lipase. Many cases of sus-

NOTE.—It is a great pleasure to thank members of the hospital staff, and especially Drs. K. M. Wilson and H. A. Stevenson of the Obstetrical Department, for many courtesies and valuable assistance.

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# BULLETIN

OF

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## ON THE TREATMENT OF LEUKÆMIA WITH BENZOL.

By LEWELLYS F. BARKER, M. D., and JAMES H. GIBBES, M. D.

(From the Medical Clinic of The Johns Hopkins Hospital and University.)

Previous to von Kórányi's<sup>1</sup> communication on the use of benzol in the treatment of leukæmia and other disorders of the blood-forming organs, the interest in this chemical was essentially industrial in nature. In medical literature it had been considered by Santesson<sup>2</sup> in 1897, and by Selling<sup>3</sup> in 1910, it having been called to the attention of these authors through toxic symptoms in people whose occupations exposed them to its action. Both Santesson and Selling followed their clinical observations by the experimental production of benzol poisoning in animals. These clinical and experimental investigations were originally far from the field of therapy, but in the light of a new interpretation, have been the means of discovering what may turn out to be an efficacious drug in the treatment of certain blood-diseases. Von Kórányi attributes his decision to try benzol in leukæmia to Selling's work, and this naturally brings the observations of the latter author again into prominence, rendering a brief review of his findings desirable.

Three cases which were clinically classified as hæmorrhagic purpuras occurred in girls working in a canning factory near Baltimore. Their specific employment brought them into constant contact with the fumes of benzol which evaporated from a mixture used in soldering the tops on the cans. These

young girls, each of them about fourteen years of age, entered the medical clinic of The Johns Hopkins Hospital with complaints of "spots on the body and giddy spells." Among their symptoms may be mentioned weakness, abdominal pain, and bleeding from the mucous membranes. Physical examination showed pallor, purpuric spots, and hæmorrhages in the retinae. The blood-pictures were characterized by marked secondary anæmia and leucopenia, the white blood cells being as low as 140 per cmm. in one of the patients. The white blood count in this particular patient continued to fall after her admission to the hospital, i. e., in spite of the fact that the exciting cause had been removed. This persistence of effect after benzol is withdrawn has been seen in its use in leukæmia, and is of considerable importance in determining at what point in the fall of the leucocytes its administration should be stopped. Cases in which the drug has been discontinued when the leucocytes had reached 12,000 to 14,000, have subsequently shown a normal count or even a leucopenia. Two of the patients reported by Selling died. Clinically, they had shown very extensive purpura and bleeding from the mucous membranes, and it is of particular interest to note that blood platelets were almost entirely



about 1000 per cmm. and reduced to 2500 per cmm. in the other. Duke's<sup>4</sup> recent suggestion that a deficiency of platelets is responsible for certain forms of hæmorrhagic disease is of interest in this connection. The differential counts revealed a relatively marked decrease in the polymorphonuclear cells, while the lymphocytes were relatively increased. At autopsy, the bone marrow was found to be aplastic, and a note was made that in one of the cases the spleen showed areas of hyaline necrosis affecting the Malpighian corpuscles. The other findings were incidental to the anemia or had no apparent bearing upon the condition under investigation. The third patient presented symptoms entirely in accord with the other two, except that the gastro-intestinal manifestations seem to have been somewhat more prominent, as was evidenced by the anorexia and vomiting. Her anemia was much less profound, the hæmoglobin being 54 per cent; the leucopenia was of a low grade (w. b. c. 4400), and her platelet count was 104,000 per cmm., this last corresponding with the fact that her purpuric eruption was not very extensive. Thus, Selling in his article described, as the clinical evidences of benzol poisoning, giddiness, headache, gastrointestinal symptoms, purpura, anemia, and leucopenia. And these, as we shall see, are the danger signals that we should be on the lookout for, now that the chemical has become a therapeutic agent.

The experimental investigations which followed the appearance of these cases consisted in the subcutaneous injection of benzol into rabbits, in doses "suitable to produce chronic or subacute poisoning." A diminution in the white blood cells was the striking result obtained, while the red blood cells were much less readily affected. But after a prolonged exhibition of the drug a severe secondary anemia was produced. Post mortem examination confirmed this somewhat selective action, the bone marrow disclosing a great diminution in the polymorphonuclear cells and degenerative changes in the myelocytes, the red blood cells remaining practically unaffected. This action of benzol in certain dosage, destroying white blood cells or inhibiting their formation in the leukopoietic fissures, without injury to the red cells or to the erythropoietic apparatus, was clearly before the profession in 1910, and it seems but a short step from this to the therapeutic use of benzol in leukemia.

In connection with the poisonous action of benzol, a few instances of recorded intoxication may here, appropriately, be mentioned. Santesson's and Selling's cases have been referred to above. Schultze<sup>5</sup> reports an instance of three men who were poisoned while working with a machine from which they inhaled the fumes of benzol. One of the three died. Beisele<sup>6</sup> tells of a workman who was painting the inside of a vessel with a solution containing 10 per cent benzol when he was taken suddenly ill with pain in the head and vertigo, and shortly passed into a drunken-like stupor. He suffered for some time from memory disturbances, but gradually recovered. Finally Duke<sup>7</sup> employed benzol experimentally as a means of varying the platelet count in rabbits. He found that with doses sufficiently large to prove fatal in about eleven days, there was an initial rise in the number of platelets followed by a rapid fall, amounting almost to dis-

appearance in some instances. This change was accompanied by a severe anemia and leucopenia. In smaller doses, benzol acted as an irritant, there being a steady increase in the platelet count. This platelet destruction should be kept in mind as a possible explanation of the purpura and hæmorrhages from the mucous membranes that are seen in cases of benzol poisoning.

In July, 1912, von Korányi reported the first case of splenomyelogenous leukemia in the treatment of which benzol was used. He states that he was led to the institution of this therapy through the pharmacological effects of the chemical as illustrated in Selling's experiments, *i. e.*, an inhibition of the white blood corpuscle-forming organs and a neutral effect or a stimulant action upon the production of red blood cells and hæmoglobin. A brief recital of von Korányi's case will serve to outline an apparently typical course under this mode of treatment. His patient was a woman, 32 years of age, who entered his clinic on the 30th of January, 1912, complaining of weakness and of enlargement of the abdomen. On examination, in addition to the pallor, the spleen was found to reach one hand's breadth below the umbilicus and to extend medialward, to the mid-line. There was tenderness over the sternum. At this time the blood examination showed: r. b. c., 3,100,000; w. b. c., 220,000; and the differential count revealed 16 per cent myelocytes. There was an exposure to X-rays on February 1. On February 6, the white blood cell count was 160,000. On February 16 it was 200,300, and on that date benzol was begun in doses of 3 gm. daily, the dosage being increased on March 1 to 4 gm. a day. The drug was continued in this quantity throughout its administration. The blood counts on subsequent dates were:

February 23, white blood cells.....	= 173,000
March 1, " " " .....	= 198,000
March 22, " " " .....	= 120,000
April 4, " " " .....	= 65,000
April 23, " " " .....	= 19,600
May 12, " " " .....	= 12,000
May 15, " " " .....	= 8,000

The drug was then discontinued. At the beginning of the course the red blood cells fell to 3,000,000, while at the end they were found to be 4,000,000. The spleen was considerably reduced in size, and the patient's general condition was markedly improved. The last examination which is reported was made on July 1, approximately six weeks after treatment was stopped, and the number of white blood cells had not changed. From his experience with the drug, von Korányi formulates the following conclusions:

1. Benzol first tends to increase the white blood cells, but shortly leads to an improvement in the leukæmic condition. The fall in the white blood count usually begins at the end of the second week or at the beginning of the third week of therapy, the decrease at first being slow and then quite rapid. The general condition of the patient is improved just as with X-rays and other forms of treatment.

2. Benzol acts more slowly than X-rays but some patients improve under its administration who do not respond to the usual therapy. Previous or concomitant applications of the X-ray seem to hasten the action of the new drug.

3. The drug can be safely given in doses of 4 gm. daily, and its administration with equal parts of olive oil seems to lessen the tendency to produce unpleasant symptoms, such as heart-burn, eructations, and vertigo.

4. Benzol seems to be efficacious in the treatment of polycythemia with splenic enlargement, one case showing a fall in red blood cells from 9,000,000 to 6,700,000 after three weeks of treatment.

The rapid accumulation of new data on this subject has tended to confirm, in almost every detail, von Korányi's original statements. There are some instances in which the transient increase in the leucocytes does not take place, but the evidence to date seems to indicate that this rise is the rule and that its failure to appear represents the exception. Shortly after von Korányi's report, Királyfi<sup>8</sup> published from the same clinic eight cases in which benzol had been used. In some, the dosage had been increased to 5 gm. daily without untoward effects, and we have used, in the case we are about to report, the drug in this quantity over a long period with no unpleasant manifestations. Királyfi's cases were grouped as follows: Five cases of splenomyelogenous leukæmia, one case of lymphatic leukæmia, one case of pseudo leukæmia, and one case of polycythæmia. One of the splenomyelogenous cases left the hospital prematurely with a leucocyte count of about 100,000, but the others of this type showed improvement in their general condition and a fall of their white blood cells to normal. The patient with lymphatic leukæmia likewise showed a marked reduction in the total leucocyte count, from 140,000 to 8000, but the differential count still showed 63 per cent of lymphocytes at the end of the treatment. The patient with pseudoleukæmia had a leucocyte count of 24,100, the formula being normal. The glandular enlargements were successfully diminished by the aid of arsenic and X-rays. However, the count of the white blood cells still remained high. For this reason, benzol was given, and in about six weeks the count had been reduced to 12,000. The polycythæmia was decreased from approximately 9,000,000 to 6,000,000 under the influence of the drug. The patient then left the hospital; when seen a short time later the number of his red cells had again increased.

Billings,<sup>9</sup> of Chicago, has recently reported five cases in which he used benzol, four of his patients suffered from myelogenous leukæmia, one of them from lymphatic leukæmia. This last author notes essentially the same changes as reported by von Korányi, but draws attention to the entire disappearance of myelocytes from the blood in one of his patients, whose white count had been reduced from 191,000 to 3600. The percentage of myelocytes has been uniformly less after the total cell count has decreased—as one would expect from similar experiences with arsenic. But it is decidedly unusual for the myelocytes wholly to disappear from the peripheral blood. It might be interesting to speculate as to the significance of this finding; does it represent a return of the bone-marrow function to normal or are we dealing simply with a temporary paresis of its activity? Billings' patient with lymphatic leukæmia behaved similarly to Kir-

ályfi's in that the total leucocyte count reached normal while the percentage of mononuclear cells remained high.

Gouget<sup>10</sup> presents a most satisfactory review of the literature on this subject, having collected six cases in addition to those reported by von Korányi and Királyfi. He tabulates these cases, indicating the fall of leucocytes under treatment, as follows:

Kovacs <sup>11</sup>	.....	white cells fell from	350,000 to 12,000
Stern <sup>12</sup>	.....	" " "	264,000 to 12,000
Tedesko <sup>13</sup>	.....	" " "	120,000 to 11,000
Eppinger <sup>14</sup>	.....	" " "	300,000 to 7,000
Stein <sup>15</sup>	.....	" " "	225,000 to 6,000
Wachtel <sup>16</sup>	.....	" " "	182,000 to 13,000

Tedesko's patient was a woman, 53 years old, suffering from lymphatic leukæmia, the blood showing on admission 84 per cent of small mononuclear elements. Under treatment, the leucocyte count fell to 11,000, the percentage of mononuclears remaining practically unchanged, while the red blood cells underwent a remarkable increase—from 975,000 to 3,770,000. It is noteworthy that the failure of benzol materially to change the differential blood formula in this case of lymphatic leukæmia is in keeping with the findings of other authors. On the other hand, the percentage of myelocytes has been considerably reduced along with the fall in the total leucocyte count, in every case of myelogenous leukæmia treated by this method.

We thus have from the literature reports of eighteen cases in which benzol has been used. These eighteen patients represent the following conditions:

Splenomyelogenous leukæmia	.....	13 cases
Lymphatic leukæmia	.....	3 "
"Pseudo leukæmia"	.....	1 case
Polycythemia with splenic tumor	.....	1 "

We, ourselves, desire now to add a case of splenomyelogenous leukæmia that responded in the usual manner to benzol therapy. A white male, 57 years old, referred to one of us by Dr. Randolph, of Charlottesville, Va., entered the medical service of The Johns Hopkins Hospital on November 23, 1912, complaining of nervousness, insomnia, and general psychasthenic symptoms. On a previous admission, May, 1906, he had presented similar complaints, his condition at that time having been diagnosed as neurasthenia. The blood count, in this earlier history, revealed: red blood cells 5,200,000, white blood cells 6500. He was in exceptionally good health after leaving the hospital in 1906 until the onset of the symptoms which led to his present admission. The *family history* is unimportant. In his *past history*, the positive points are: malarial fever at 15 years of age; four gonorrhœal infections about 20 years ago with a resulting chronic prostatitis, a chancre 19 years ago for which he was treated and "pronounced cured," and a marked history of alcoholism and tabagism. The symptoms which he considers as due to the *present illness* began approximately two months before his entrance to the hospital. They consisted of extreme nervousness, anorexia, insomnia and marked depression with feelings of general inefficiency.

The *physical examination* was entirely negative. The spleen was not palpable on admission, has not been felt at any time since, and the splenic dullness was not increased. There was no general glandular enlargement.

On November 24, 1912, the blood picture showed:

Red blood cells .....	3,672,000
White blood cells .....	345,000
Hæmoglobin (Sahli) .....	65

Differential count with Ehrlich's stain made by Dr. Sidney R. Miller gave the following formula:

	Cells counted.	Percentage.
Polymorphonuclear neutrophils .....	387	60.75%
Polymorphonuclear eosinophiles .....	5	0.75%
Polymorphonuclear basophiles .....	12	1.99%
Small mononuclears .....	35	5.48%
Large mononuclears .....	17	2.65%
Transitionals .....	14	2.19%
Neutrophilic myelocytes .....	158	24.79%
Eosinophilic myelocytes .....	3	0.47%
Basophilic myelocytes .....	4	0.62%
Myeloblasts .....	2	0.31%
	637	100.00%

In making the count, 8 normoblasts were seen and 1 megaloblast.

The Wassermann reaction was positive on November 30, 1912.

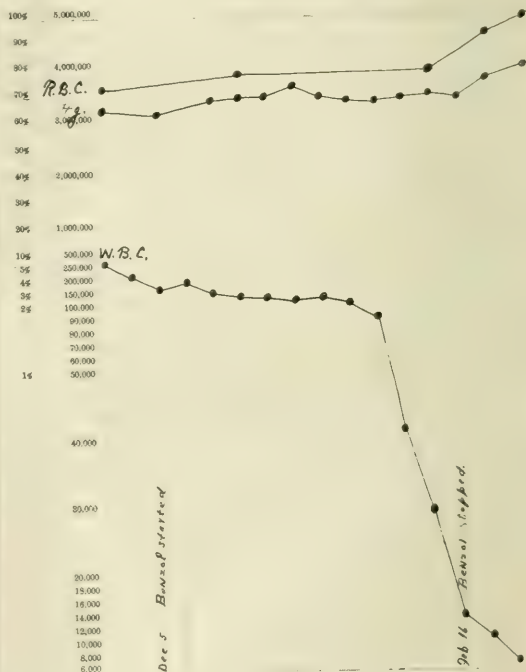
X-rays of long bones were negative on November 29, 1912.

The urine presented fairly constant findings throughout. Quantity, 1800 to 2000 cc. for 24 hours; specific gravity, 1018 to 1020; reaction, acid; a granular sediment; hyaline and granular casts and large numbers of uric acid crystals were seen on microscopic examination. Dr. Guthrie made an especial examination of the urine for Bence-Jones body and found it present. In a recent paper Boggs and Guthrie<sup>17</sup> mention three cases of lymphatic leukaemia from the literature which showed a Bence-Jones proteinuria, while nine cases of lymphatic leukaemia and fourteen of myelogenous leukaemia are listed in which this condition was absent. As far as is known to us, our case is the only one of this variety of leukaemia in which the urine has contained the Bence-Jones body.

*Treatment and Course.*—From November 24 to November 26, the patient received no treatment other than absolute rest in bed. On the latter date, Fowler's solution was begun in doses of 3 minims three times a day, increasing one minim per dose each day. This treatment was discontinued on December 5. On November 29, X-ray pictures were taken of the tibia and fibula of one leg, this being the single exposure to X-rays. On December 4, on account of the positive Wassermann an intravenous injection of 0.3 gm. of neosalvarsan was given. On December 5, the white blood cells were 191,000, and on this day the benzol treatment was started; 2 gm. were given the first day, and the dose was increased 1 gm. each day until it reached 5 gm. The drug was then continued in this quantity until withdrawn on February 15, 1913. Five days after this treatment was started the white

blood cells rose to 210,000. They then began to fall, reaching 188,000 on December 16, and continued to fall slowly until January 9, when the reduction became much more rapid. This was almost six weeks after the beginning of the treatment. In another six weeks, the white blood count had fallen to 10,200. For fear of causing too marked a hypoplasia of the marrow, the drug was discontinued at this point, and one week later the leucocyte count was 7800. During the period of treatment the red blood cells had increased from 3,600,000 to 5,000,000 and the hæmoglobin reached 82 per cent.

BLOOD CHART.



Top line = red blood cells.  
Middle line = hæmoglobin.  
Bottom line = white blood cells.

The drug was given in "5 grain" gelatin capsules, containing one-half gram each of chemically pure benzol and olive oil.

Another differential count with Ehrlich's stain was made by Dr. Sydney Miller on February 20:

	Cells counted.	Percentage.
Polymorphonuclear neutrophils .....	440	88.0%
Polymorphonuclear eosinophiles .....	5	1.0%
Polymorphonuclear basophiles .....	3	0.6%
Small mononuclears .....	10	2.0%
Large mononuclears .....	16	3.2%
Transitionals .....	22	4.4%
Myelocytes .....	4	0.8%
	500	100.0%



It was noted that there was practically a complete absence of platelets during this count. The great reduction in the platelet count is of particular interest when viewed in connection with the occurrence of a purpura in the patient. This was first noticed as a small subcutaneous hæmorrhage on the back of one of his hands. By the end of the tenth week of treatment he had a rather extensive eruption over the lateral aspects of the legs and a few spots were visible scattered over the trunk. There was absolutely no increase in the condition after this time, in fact the purpura had cleared to some extent when the patient was discharged. On February 25, the day before discharge from the hospital, the bleeding-time was found to be only one and a half to two minutes. There was no bleeding from the gums at any time, and no epistaxis. The retinae were perfectly clear when the patient left the hospital.

The *clinical notes* on the patient's condition show him to have made a steady improvement from the beginning of his treatment to the time of his discharge. The most marked subjective feature throughout was his extreme psychoneurotic state, but this became progressively better with the lowering of his white blood count. At no time during the administration of benzol did he complain of vertigo or eructations, nor was he troubled with colds or bronchitis. He did have a slight sensation of burning along the œsophagus at times, and the odor of benzol was perceptible in his breath.

Our case, as will have been seen, is in accord with previous reports, and so demands but little especial comment. The course of benzol administration extended over approximately eleven weeks, during which period the total number of white blood cells returned to normal, the red blood cells increased from 3,600,000 to 5,000,000, the hæmoglobin changed from 65 per cent to 82 per cent, and the patient's general condition showed definite improvement. In as far as we can judge of this new line of therapy in leukæmia from the observation of the patient reported, we share the belief of most authors as to its efficacy in reducing the white blood cells, and in leading to an associated subjective improvement of the patients. Our patient progressed in a satisfactory manner with the exhibition of benzol alone, but we feel that the possible value of other accessory measures, such as X-rays, arsenic, thorium X, and radium, in the therapy of leukæmia should be kept in mind. Pappenheim's<sup>18</sup> recent criticism of the benzol treatment, based upon a theoretical consideration of Selling's work and an attempt to apply some experimental studies made by himself to clinical medicine, has been replied to by von Korányi.<sup>19</sup> The latter author holds that the production of definitely noxious manifestations in rabbits and anatomical lesions of the kidneys, liver, lungs, and spleen, by relatively immense doses of benzol, does not necessarily imply that similar effects follow upon the use of the drug as it is now therapeutically employed in leukæmia. Von Korányi incidentally mentions that one of his patients is, at the present time, apparently well, ten months after the discontinuation of treatment. Tedesco<sup>20</sup> likewise replies to Pappenheim, stating that he has observed no bad results clinically, and warn-

ing against such criticisms as tending to prevent an adequate testing of the new drug. The ultimate place of benzol in the treatment of leukæmia, polycythæmia, and Hodgkin's disease can be determined only through further studies which include careful clinical observations.

Finally, we wish to emphasize the facts, first, that benzol does possess dangerous toxic properties; second, that its clinical effects are not yet clearly understood, and, third, that the greatest care should be exercised in its administration. A studious regard for the dosage as thus far determined, a watchfulness for the manifestations of poisoning that are well defined and easily detected, and a willingness to employ other measures in conjunction with this drug, are means that will serve to give the new treatment a fair trial and prevent its falling into an undeserved disrepute. Certainly, no patient should be treated by benzol unless he can be kept under continuous close observation; for the present, therefore, it may be well to restrict its use to the treatment of patients in hospitals, rather than to run the risks attendant upon its extension to domiciliary practice.

*Addendum.*—On April 9, 1913, approximately seven weeks after the benzol treatment was discontinued, the patient returned to the hospital for salvarsan. He had received no medication in the interim. His blood count at this time showed:

Red blood cells .....	4,096,000
White blood cells .....	6,800
Hæmoglobin (Sahli) .....	76%

#### Differential count (Wilson's stain):

	No. cells.	Percentage.
Polymorphonuclear neutrophiles .....	147	73.5%
Polymorphonuclear eosinophiles .....	2	1.0%
Polymorphonuclear basophiles .....	2	1.0%
Small mononuclears .....	7	3.5%
Large mononuclears .....	4	2.0%
Lymphocytes .....	25	12.5%
Transitionals .....	5	2.5%
Myelocytes, neutrophiles .....	6	3.0%
Myelocytes, basophiles .....	2	1.0%
	200	100 %

He was given 4.5 gm. of neosalvarsan intravenously and iron in the form of Blaud's pills. When discharged on April 26, his blood count was:

Red blood cells .....	4,800,000
White blood cells .....	7,000
Hæmoglobin (Sahli) .....	79%

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## BENCE-JONES PROTEINURIA IN LEUKÆMIA: A REPORT OF FOUR CASES: THE EFFECT OF BENZOL ON THE EXCRETION OF THE PROTEIN.

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The occurrence of Bence-Jones proteinuria in multiple myeloma is well known. That it may occur in conditions other than myelomatosis has also been pointed out by various observers and the writers have recently reviewed the literature on this particular aspect of the subject.<sup>1</sup> Leukæmia is one of the diseases with which the excretion of this unusual protein may be associated, but the phenomenon has been noted in only four instances, and only in the chronic lymphatic form of the disease, although many cases of all the various types have been repeatedly examined. In a series of fourteen leukæmic patients (acute lymphatic, 2; chronic lymphatic, 4; acute myeloid, 3; chronic myeloid, 5) which has recently been carefully studied, the Bence-Jones body has been found in the urine in four instances (chronic lymphatic, 1; chronic myeloid, 3). Since this is the first observation of Bence-Jones proteinuria in chronic myeloid leukæmia and also as it has been so rarely observed in any form of the disease, it has seemed advisable to report the cases in some detail, especially since these cases seem to furnish additional evidence in support of the belief that a causal relationship exists between pathological changes in the bone marrow and the excretion of this protein.

**CASE I.\***—The patient, æt. 57, male, white, a clerk, was admitted November 23, 1912, and discharged February 25, 1913.

**Diagnosis.**—Chronic myeloid leukæmia. There was a previous admission in May, 1906, for neurasthenia, when the blood count was normal.

**Past History.**—Malaria 42 years ago. Lues 20 years ago. Fairly constant drinker. Several attacks of gonorrhœa in past 20 years, with resulting chronic prostatitis.

**Present illness.**—Began the last of September, 1912, when he had a nervous shock, since which time he has felt run down and has lost 7 pounds in weight. There was anorexia, insomnia and depression, with physical weakness, indigestion, constipation and nycturia.

**Physical Examination.**—Patient was well nourished. Pupillary reactions normal. No enlargement of thyroid or cervical lymphatic glands. Thorax well formed. Heart and lungs normal. Abdomen apparently normal. Liver and spleen not enlarged. Stools normal.

\* This case is reported from the clinical and therapeutic standpoint by Drs. Barker and Gibbs in this issue of the Johns Hopkins Hospital Bulletin.

**Blood Examination.**—R. B. C., 3,672,000; W. B. C., 345,000; Hb., 65%; Color index, 0.89; Differential leucocyte count:

Polymorphonuclear neutrophiles .....	60.75%
Polymorphonuclear eosinophiles .....	0.75%
Polymorphonuclear basophiles .....	1.99%
Small mononuclears .....	5.48%
Large mononuclears .....	2.65%
Transitionals .....	2.19%
Myelocytes, neutrophilic .....	24.79%
Myelocytes, eosinophilic .....	0.47%
Myelocytes, basophilic .....	0.62%
Myeloblasts .....	0.31%

Nucleated R. B. C.—8 normoblasts and 1 megaloblast seen in counting 637 W. B. C.

Wassermann reaction positive. Salvarsan 0.3 gm., intravenously on December 4. Reaction at time of discharge still positive. The X-ray examination revealed no abnormality in the long bones.

**Benzol Therapy.**—Started December 5, 2 gm. benzol per diem in four doses by mouth, increasing by 1 gm. daily until 5 gm. was reached and continued at this dosage. After four weeks of benzol treatment the W. B. C. count had fallen to 166,000. In the 7th week the W. B. C. count was 96,000; 8th week, 42,000; 9th week, 28,000; 10th week, 14,000; 12th week, 7,800. At this time, when he was discharged, the blood examination showed: R. B. C., 5,000,000; Hb., 82%; Color index, 0.8; Differential W. B. C. count:

Polymorphonuclear neutrophiles .....	88.0%
Polymorphonuclear eosinophiles .....	1.0%
Polymorphonuclear basophiles .....	0.6%
Small mononuclears .....	2.0%
Large mononuclears .....	3.2%
Transitionals .....	4.4%
Myelocytes .....	0.8%

No nucleated R. B. C. seen. Platelets practically absent. The patient's subjective and objective symptoms seemed to be greatly improved. He is to return for observation.

**Characteristics of the urine.**—Total amount, 1650 cc.; clear, amber; acid; sp. gr., 1018; heavy, yellow, granular sediment with coarse uric acid crystals; no sugar; protein present, too small in amount for Tsuchiya estimation; total chlorides, 10 gm. Microscopically:—numerous uric acid crystals; many clumps of amorphous urates; many finely and coarsely granular casts; a few epithelial cells; no R. B. C. or W. B. C.; occult blood test (guaiac), negative.

**Functional renal tests** were reported by Dr. W. A. Baetjer as follows: Phenolsulphonephthalein output, 27% in first hour; 28% in second hour; or 55% in two hours (slightly below normal).

Lactose, six hours required for excretion (slightly delayed). KI normal; total excretion in less than 48 hours. Rest nitrogen (blood serum), 0.42 gm. per litre (normal). Sodium chloride-excess normally excreted; excreting 8-10 gm. daily on constant diet; increase of 7 gm. given; this excess was excreted by increased concentration in the urine without increase in fluid output. *Conclusion:* Slight impairment of renal function of vascular rather than tubular origin, as indicated by the slight delay in lactose excretion (Schlayer), while the tubular tests, NaCl and KI gave normal results.

*Protein Tests.*—The filtered urine gave no precipitate with acetic acid in the cold, nor when dropped into a beaker of distilled water, showing the absence of mucin, nuclealbumin and globulin. The unacidified urine gave no precipitate when heated to 60° C. When the urine, slightly acidulated with dilute acetic acid (5%) was heated slowly, precipitation began at 51° C. and was apparently complete at 60° C., the urine being turbid and the precipitate settling out in flocculi on standing. This precipitate was almost completely soluble on boiling, but reappeared when cooled, dissolving again on boiling. A fresh, acidulated specimen, heated to 60° C. for one hour and then cooled, showed a precipitate as above, the filtrate from which remained clear on reheating to 60° C. for one hour and cooling; showing the complete removal of the protein precipitable at this temperature. The same specimen, heated slowly from 60° to 90° C. and eventually boiled, gave no further precipitation either immediately or on cooling. Spiegler and biuret tests applied to this specimen were also negative, demonstrating the absence of serum albumin. The layer test with concentrated nitric acid in the cold gave a sharp white ring at the line of junction. With a few drops of dilute nitric acid (25%) in the cold, a turbidity was produced which almost completely disappeared on boiling and reappeared on cooling. With two volumes of saturated ammonium sulphate solution there was a flocculent precipitate, the filtrate from which did not give a biuret reaction, while the precipitate was readily soluble in water, from which it could be reprecipitated on further addition of two volumes of saturated ammonium sulphate solution. For the further study of the precipitate obtained by heat, the urine for two days (3.4 litres) was filtered through plain paper to remove the sediment, the clear filtrate slightly acidified with acetic acid and heated to 60° C., in a water bath over night. The resulting dark brown, flocculent precipitate was collected by decantation and washed repeatedly with distilled water; it was then centrifugalized to a small volume, suspended in 20 cc. of water and a few drops of 5% sodium carbonate solution added, when on heating to 45° C. the precipitate was completely dissolved, yielding a clear, dark brown solution. This was dialyzed in a collodion sac against running water for 24 hours. The clear, slightly brownish solution was neutral to litmus; gave no precipitate on boiling; became slightly cloudy on the addition of dilute acetic acid in the cold; and on warming this acidified fluid there was complete precipitation at 60° C., and partial resolution on boiling. The addition of a few drops of calcium chloride solution to the acidulated dialyzate intensified the sharpness of the reaction, so that solution was complete at the boiling point with precipitation on cooling. Another portion of the dialyzate acidified with dilute nitric acid (25%) yielded similar results.

The total urine of two other days (3 litres) was treated with ammonium sulphate to two-thirds saturation and the brownish-yellow precipitate collected by decantation. The supernatant fluid was filtered and tested by heat and acetic acid, nitric acid in the cold, Spiegler and biuret, and found free from protein. The ammonium sulphate precipitate was redissolved in water and again precipitated by two-thirds saturation with ammonium sulphate, this process being repeated three times. The final precipitate was dissolved in water, placed in a thin collodion sac and dialyzed against running water for 24 hours. Another por-

tion of the precipitate was dialyzed in a similar manner against distilled water for 72 hours. At the end of this time, the water outside the sac was found free from protein by the Spiegler and biuret tests, showing that none of the protein passed through the sac. The portion dialyzed against running water, when faintly acidified with 5% acetic acid, gave a slight turbidity in the cold, a flocculent precipitate at 60° C. and partial solution on boiling, which became complete on the addition of a few drops of calcium chloride solution.

The further course of this patient under treatment is of considerable interest as furnishing experimental evidence of the relation of the bone marrow or blood forming centres to the excretion of the Bence-Jones body. The urine was followed in repeated and careful examinations over a period of about twelve weeks. The findings were practically constant until the benzol treatment was begun. There was a moderate polyuria, the urine being of normal specific gravity, acid in reaction, with heavy precipitate of urates and uric acid. No sugar was present and no protein other than the Bence-Jones, and this in small amounts. Microscopically there were a few finely and coarsely granular casts. The total chlorides were followed for a week, showing an output which varied from 9.6 gm. to 15.2 gm., with an average of 11.6 gm. per diem. With the development of the effect of the benzol treatment on the blood picture, there was concurrent diminution in the excretion of the Bence-Jones protein, until during the last few days of observation it was no longer demonstrable. It is especially to be remarked that with the disappearance of the Bence-Jones body, there was no evidence of any other type of protein excretion, the urine remaining free from albumin, nor was any true albumose (proteose) detected by the Salkowski method either at this time or during the period before the benzol treatment was begun. During the benzol period the urine became gradually more concentrated, dropping to one-half the original volume, darker in color, more strongly acid, and very rich in uric acid and urates, which began to precipitate immediately after voiding, giving the urine a milky appearance. At no time was there any spontaneous precipitation of the Bence-Jones protein, not even in specimens kept for several months over chloroform.

In connection with the foregoing, detailed study, we should like to note briefly a second case, in which we were able to make only one examination of the urine, as the patient, who came from a long distance for diagnosis, was in the hospital only one night.

*CASE II.*—The patient, a white man, aet. 33, married, a carpenter, was admitted January 16, 1913, and discharged January 17, 1913.

*Diagnosis.*—Chronic myeloid leukaemia.

*Complaint.*—Enlarged spleen and weakness.

*Family History.*—Unimportant.

*Past History.*—No serious illness in childhood or at any time until the present.

*Present Illness.*—Began about fifteen months before admission with anorexia, indigestion and pain in the epigastrium, lasting about three months. After the subsidence of these symptoms the patient noticed a lump in the left side which increased steadily in size for five or six months, at which time there developed a severe pain over the region of the mass. This lasted about three weeks and necessitated the patient's sitting up constantly in a chair. At this time the mass almost filled the abdomen and extended into both flanks, but has since become smaller. There was oedema of the legs and fulness in the abdomen which has diminished in the last five months. Transient attacks of pain have recurred from time to time.

*Physical Examination.*—The patient was well nourished; color slightly yellowish; pupils and eye movements normal; slight



general glandular enlargement. Lungs normal. Heart normal. Abdomen very prominent, especially over the left half which was filled by a large firm spleen, extending 20 cm. below the ensiform cartilage in the midline and 25 cm. in transverse diameter. The liver was not appreciably enlarged. No ascites. The superficial abdominal veins were somewhat distended. Blood pressure normal.

*Physical Examination.*—R. B. C., 3,072,000; W. B. C., 506,000; Hb., 50%; Color index, 0.83; Differential leucocyte count:

Polymorphonuclear neutrophiles	50.3%
Polymorphonuclear eosinophiles	1.5%
Polymorphonuclear basophiles	0.2%
Small mononuclears	5.6%
Large mononuclears	6.6%
Transitionals	3.3%
Myelocytes, neutrophilic	27.3%
Myelocytes, eosinophilic	3.2%
Myelocytes, basophilic	0.6%

Nucleated R. B. C. 2 normoblasts seen in counting 500 white cells.

*Urinary Examination.*—The single specimen of urine examined was yellow, slightly turbid, acid in reaction, sp. gr. 1014. No sugar. Small amount of protein present. Microscopically: flocculent sediment showing a few epithelial cells and granular casts. The acetone, occult blood and diazo tests were negative. On more detailed examination of the protein it was found that there was no globulin or serum albumin present. With dilute acetic acid in the cold, a precipitate was obtained which yielded, after hydrolysis, qualitative tests for a reducing body and for sulphuric acid and was apparently the so-called Mörner's body. After complete removal of this body, further tests were carried on as follows: The remaining urine gave a characteristic precipitate at 60° C. with partial resolution on boiling and reprecipitation on cooling. The filtrate from this reaction did not give a further precipitate on heating to 60° C. nor at the boiling point. The precipitate was readily soluble in dilute sodium carbonate solution on gentle warming at a low temperature and gave the reactions for Bence-Jones protein in alkaline solution. With dilute nitric acid (25%) there was an initial turbidity in the cold, increased on warming, partial clearing on boiling, and reprecipitation on cooling. The addition of two volumes of saturated ammonium sulphate solution gave a flocculent precipitate, soluble in water and on dialysis. It seems evident, therefore, that this urine contained Bence-Jones protein and Mörner's body.

CASE III.—The patient, a colored man, aet. 60, married, a laborer, was admitted July 2, 1913, and at the time of writing, August 12, 1913, is still in the hospital.

*Diagnosis.*—Chronic myeloid leukaemia.

*Complaint.*—Swelling of legs, shortness of breath, and occasional choking sensation in throat.

*Family History.*—Unimportant.

*Past History.*—Gonorrhoea at 26; winter cough for several years. Hemorrhoids which have bled occasionally at intervals of six to twelve months during past fifteen years. Nycturia for three years. Loss of fifteen pounds in weight.

*Present Illness.*—Health good until seven months before admission, when he began to have dyspnoea on exertion and swelling of the ankles at night. This condition cleared up on resting, but returned when he went back to work. As a result, he has suffered intermittently until three weeks ago, when he stopped work. The dyspnoea and oedema increased up to one month ago, when the patient began to have orthopnoea as well. For the past four months he has had morning cough, with yellowish, blood-tinged expectoration, and for the last two months, night sweats once or twice weekly. Giddiness for three months. Diarrhoea for four days prior to admission.

*Physical Examination.*—Some emaciation. Pallor of lips and

mucous membranes. Fulness of superficial veins of arms, also of the veins of the lateral thoracic, umbilical and hypogastric regions. Arcus senilis. Pupillary reactions normal. Pyorrhoea and dental caries. Rather spongy gums. Slight general glandular enlargement.

*Lungs.*—Slight impairment at left apex and at bases behind, otherwise hyper-resonant throughout. Moist râles heard over both lungs.

*Heart.*—Somewhat enlarged; marked arrhythmia; many extra systoles; slight systolic blow at apex, transmitted outward. Very marked sclerosis of peripheral arteries.

*Abdomen.*—Liver 6½ cm. below right costal margin, firm. Some shifting dullness in flanks. Oedema of both legs. Knee joints not obtained. Plantar response normal.

*Blood Examination.*—July 15, 1913, R. B. C., 3,320,000; W. B. C., 336,000; Hb., 49% (Sahli); Color index, 0.73; Differential leucocyte count:

Polymorphonuclear neutrophiles	53.6%
Polymorphonuclear eosinophiles	4.4%
Polymorphonuclear basophiles	0.4%
Small mononuclears	3.2%
Large mononuclears	0.8%
Transitionals	0.4%
Myelocytes, neutrophilic	36.4%
Myelocytes, eosinophilic	1.2%

Nucleated R. B. C., both normoblasts and intermediates seen.

*Wassermann reaction* negative.

*Blood Pressure.*—140 mm. Hg. (Tycos).

*Temperature.*—Gradually rose in first four days to 102° F. and then gradually fell to normal with an occasional slight elevation, but on July 23d it rose to 100.6° F. and on the 24th reached 103° F. Gradual fall since then.

*Pulse.*—Irregular, but relatively lower than temperature throughout.

*Treatment.*—Rest in bed; "cardiac diet"; fluid intake limited to 1500 cc.; course of twelve doses of tincture of digitalis; 1 cc. four times daily, begun July 4th; benzol with olive oil in one gm. doses by mouth, begun twice a day on July 29 and gradually increased until five doses were given daily. Under the benzol therapy the white blood cells fell to 230,400 on August 2 but two days later, had risen to 294,000. On August 7 the count was 202,000 and on the 10th, 210,000.

*Urine.*—Total specimens of the patient's urine were examined for fifteen consecutive days before the benzol treatment was begun, during which time the following characteristics were noted.

*Color.*—Yellow to orange, often cloudy.

*Amount.*—In twenty-four hours, 315 to 1475 cc., gradually increasing in volume; average 950 cc.

*Specific Gravity.*—1008 to 1011; average 1009.

*Reaction.*—Acid.

*Sugar.*—Absent.

*Protein.*—Present.

*Total Chlorides.*—4 gm.

*Urobilin.*—Present.

*Indican.*—Present.

*Microscopically.*—Hyaline and granular casts; cylindroids; mucous shreds; epithelial cells; urates and uric acid crystals.

*Occult Blood Test.*—Negative.

Application of the same tests to establish the nature of the protein, as used in Cases I and II, showed that minute traces of serum albumin were excreted on seven occasions, but could not be detected at the other examinations, while Mörner's body and the Bence-Jones protein were constantly present. Although all three types of protein were too small in amount for ordinary quantitative estimation by the Tsuchiya method, judging from the intensity of the reactions and the amounts of pre-

cipitate obtained, serum albumin, when present, was least in amount. Mörner's body next, and the Bence-Jones protein relatively more abundant. No albumose (proteose) was found by the Salkowski method and globulin was absent throughout.

After benzol was started on July 29 the urine was followed carefully over a period of two weeks, during which time no material changes were noted. The three proteins found before were still present in small, but variable amounts and no others were detected. The persistence of the Bence-Jones body after two weeks of benzol therapy was not considered surprising as the white blood count was still over 200,000.

**CASE IV.**—The patient, a white man, married, a lumberman, was admitted June 12, 1913, and discharged July 5, 1913.

**Diagnosis.**—Chronic lymphatic leukæmia.

**Complaint.**—Swelling of glands of body.

**Family History.**—Unimportant.

**Past History.**—Had the ordinary diseases of childhood. At 22 had measles followed by a pulmonary complication, chiefly involving the left side. During the following two years he was unable to work and had constant cough with some expectoration, fever and night sweats. At the end of two years he went back to work in the woods and has been able to continue at his occupation since then. Severe attack of bronchitis four years ago. Morning cough for last two to four years with white expectoration; none during the day. Piles for ten to fifteen years, bleeding occasionally, more freely and frequently during the past year. Denies venereal infection. His wife has had one miscarriage at two months. One child living and well. Patient drank whiskey daily for fifteen years, then to excess for five years, but has taken none during the past four years.

**Present Illness.**—Sixteen months before admission the patient had an attack of tonsillitis and quinsy, after which his tonsils remained large. In February, 1913, his tonsils still further increased in size but were not sore or tender. In March, 1913, he noticed enlarged glands at angles of his jaw, which have gradually grown in size. In May, 1913, his tonsils were removed. About June 1 he noticed enlarged glands in the axillæ and later in the groins. None of the glands have been painful or tender and at no time have they caused him any inconvenience. One week before admission he noted a swelling in the lower right axilla and a few days later purplish spots appeared over the right lumbar region.

**Physical Examination.**—Emaciation. Pallor of lips and mucous membranes. Slight jaundice. Purpuric spots over right axillary and lumbar region. Evidence of subcutaneous hæmorrhage in lower right axillary region. Very marked general glandular enlargement, the individual glands being discrete, movable, firm, and not tender. Striking hyperplasia of lymphatic tissue in pharynx and at site of tonsillectomy. Anisocoria, but normal pupillary response.

**Lungs.**—Signs of consolidation at left apex with moist râles throughout entire left side.

**Heart.**—Wide area of dullness behind the manubrium. Systolic murmur at apex, transmitted to axilla.

**Abdomen.**—Liver extended 6 cm. below the costal margin in the right mammillary line.

**Spleen.**—5 cm. below left costal margin, firm and nodular. Knee kicks present. Plantar response normal.

**Blood Examination.**—June 12, 1913, R. B. C., 2,880,000; W. B. C., 100,500; Hb., 55%; Color index, 0.96; Differential leucocyte count:

Polymorphonuclear neutrophiles .....	5.2%
Polymorphonuclear eosinophiles .....	0.4%
Polymorphonuclear basophiles .....	0.0%
Small mononuclears .....	88.0%
Large mononuclears .....	6.0%
Transitionals .....	0.4%

The Wassermann reaction was negative on June 12, but showed partial fixation (10-15%).

**Tuberculin tests** reported June 18: Calmette 1% and 5% negative; von Pirquet positive.

**X-ray Examination** of chest, June 14: Infiltration of both lungs; tuberculous consolidation of left apex.

**Temperature.**—During first week rose from normal in morning to 100° F. in p. m. Gradually the afternoon temperature fell to 99° F.

**Pulse.**—Relative tachycardia, most marked during first week, when it rose irregularly to 120, then gradually lower, but still in neighborhood of 100 on discharge.

**Treatment.**—Intravenous injection of *salvarsan* on June 14; benzol, one gm. with olive oil, in capsules by mouth; begun twice a day on June 13 and gradually increased until the patient was receiving five doses daily. Benzol discontinued on July 2. X-ray treatment three times weekly, beginning June 23. Tonics and additional feeding with eggs and cream.

During the patient's stay in the hospital his white blood count fell from 100,500 on admission to 55,000 one week later; then to 46,000 on June 24, and on July 1, four days before discharge, it had dropped to 17,600, while the red blood cells and hæmoglobin remained at practically the same level throughout the period of observation. There was marked improvement in the patient's general condition and the glands, especially those about the angles of the jaw, decreased appreciably in size and became softer in consistence.

**Urinary Examination.**—After the patient had been treated with benzol for two weeks his urine was submitted to special examination in this laboratory over a period of nine days with the following results. The urine was, as a rule, clear, and dark amber in color, becoming quite dark on standing. The amount for twenty-four hours was in the neighborhood of 500 cc. and the specific gravity varied between 1024 and 1035, the average being about 1028. The reaction was acid. Sugar was absent and protein present. The occult blood test (guaiac) was negative.

**Total Chlorides.**—6 to 7 gm.

**Microscopically** there were seen numerous cylindroids, a few hyaline and coarsely granular casts, epithelial cells, mucous shreds and uric acid crystals. For the identification of the protein, all of the tests used in Cases I and II were applied, as a result of which two general conclusions were drawn: (1) that there was no mucin, Mörner's body, albumose (proteose), globulin, or serum albumin present, and (2) that the protein present was the Bence-Jones body, as it responded characteristically to all of the tests. It was found in small, but readily appreciable amounts on the first five examinations, diminishing in quantity perceptibly day by day, until there was only a trace present on July 2. The following day it was entirely absent and on the 4th and 5th of July only the most minute trace could be detected.

**Summary:** In conclusion we should like to point out that so far as we have been able to ascertain, Cases I, II, and III, are the first reported instances of Bence-Jones proteinuria in association with myeloid leukæmia. It has never been observed in the acute forms of the disease, either lymphatic or myeloid, and, including the cases presented here, only eight times in the chronic varieties. The Bence-Jones protein alone was present in Cases I and IV of our series, while Mörner's body also was present in the other two cases, as well as serum albumin in Case III. The excretion of the Bence-Jones body was small in amount, which seems to be characteristic when it occurs apart from multiple myeloma. The chloride output was normal in Case I, which is markedly

different from the condition found in Cases III and IV and in our cases of myelomatosis and carcinomatosis.<sup>2</sup> In Cases I and IV the effect of the benzol treatment is especially noteworthy, in that a marked reduction (Case IV) or eventual disappearance (Case I) of the proteinuria and its associated polyuria, occurred, parallel to the diminution in the leucocytosis and apparent approach of the bone marrow to a more nearly normal condition. It is worth recalling in this connection that our experiments in the benzol poisoning of rabbits failed to bring about an excretion of the Bence-Jones

protein.<sup>2</sup> These cases furnish additional confirmation of the previously expressed view, that Bence-Jones proteinuria is not essentially dependent upon one disease, but is a manifestation of disturbances in the bone marrow affecting endogenous metabolism.

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## CAUTERIZATION OF "INOPERABLE" CARCINOMA OF THE CERVIX OF THE UTERUS.

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AND

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The temporary improvement following an extensive cauterization of advanced carcinoma of the cervix of the uterus has been noted by many surgeons. While the importance of an early diagnosis cannot be overestimated, the larger group, generally classified as "inoperable" cases, is not to be ignored. The result obtained by a thorough cauterization and a subsequent radical abdominal operation seems to justify a detailed report of the following case:

Gyn. No. 16152; Path. Nos. 14307 and 14418.—Mrs. J. was admitted to the clinic on October 27, 1909, complaining of "bleeding from the womb."

*Family History.*—Negative for tuberculosis and cancer.

*Personal History.*—Except for an attack of pneumonia, 24 years ago and typhoid fever, 22 years ago, the patient has enjoyed excellent health.

*Menstrual History.*—Menses began at the age of 13 years; occurring regularly every 4 weeks and lasting about 7 days; no dysmenorrhœa; no intermenstrual bleeding; meno-pause, 5 years ago.

*Marital History.*—Married 30 years; 8 children; eldest child 29 years; youngest, 12 years; 3 miscarriages, many years ago. Labors and puerperia, normal. No leucorrhœa.

*Present Illness.*—Patient began to bleed about 6 months before entering the clinic. Previously there had been no leucorrhœa or other symptoms to indicate uterine disturbance. "Spotting" (once in two or three weeks) was first noticed. Gradually, the bleeding became more profuse and about 6 weeks before being admitted, she had a very severe hemorrhage. The patient became very "dizzy" and fainted many times during the day. Following this attack, she was confined to her bed almost constantly. She consulted a physician two to three months before she came here; he told her the menses were returning. Although no examination was made, he assured her it was not cancer because the discharge didn't have a bad odor. There had been no abdominal pain, no bladder or rectal symptoms.

*Physical Examination.*—The skin is very sallow; the lips and mucous membranes show a marked pallor; the pupils are equal and react normally.

Pulse, 80 to the minute, regular, fair quality; vessel wall thickened.

Glands: inguinal glands are palpable and very hard.

Chest and abdomen, negative.

Hæmoglobin, 43 per cent (Sahl).

*Admission Note.* Oct. 29, 1909 (Dr. E. H. Richardson).—The abdomen is slightly scaphoid. There is considerable loss of subcutaneous fat. There is no abdominal tenderness. There are chains of palpable glands in both groins.

*Pelvis.*—There is a moderate relaxation of the vaginal outlet. The cervix is the seat of a large cauliflower carcinomatous growth about 6 to 8 cm. in diameter. This growth completely encircles the cervix but has not yet involved the anterior vaginal wall or bladder. The right fornix is still soft and the base of the right broad ligament is movable, although it is apparently thickened. Posteriorly and to the left side, the new growth has already involved the vaginal mucous membrane and has extended out to the pelvic wall where the tissues are fixed. The tumor mass is very friable and bleeds readily on manipulation. The body of the uterus is not enlarged. There is a profuse bloody and very offensive discharge.

On account of the free bleeding, a curettage and cauterization of the new growth was done, Nov. 3, 1909.

*Operative Note.*—Under gas anæsthesia, the examination showed that the carcinomatous growth was advanced to such a stage as to render a complete operation impossible. The cervix was greatly enlarged and large masses of carcinomatous tissue could be torn away with the fingers. It had extended quite out to the pelvic wall on the left side.

The friable portion of the growth was removed by the fingers after which the walls of the vagina were protected with moistened gauze pads. Very hot "soldering irons" were then introduced into the central portion of the growth until it was deeply cauterized on all sides. An iodoform gauze pack was then placed against the cervix.

The patient was returned to the ward and an effort made to improve the general condition by the use of tonics and general hygienic treatment. On November 14, 1909, 11 days after the cauterization, the routine examination was made preparatory to the patient being discharged. Considerable improvement was noted in her general condition and the hæmoglobin had risen to 47 per cent (Sahl). Pelvic examination showed such a "melting away and loosening up" of the carcinomatous growth that a radical operation was advised and done on the following day.



*Ether Examination and Operation.* November 15, 1909 (Dr. Kelly).—On pelvic examination, the results of the cauterization done two weeks ago were found to be remarkable. The extensive carcinomatous mass at that time occupying the vaginal vault had collapsed very markedly, and the dense induration on either side seemed to have disappeared to a great extent. There was a crater-like opening into the uterus, where the carcinoma had been burned away, so that the index finger could be introduced into the uterine cavity. The adnexæ were quite freely movable.

A hot bichloride douche was used to thoroughly flush out the interior of the uterus and vagina.

A mid-line abdominal incision was made. The pelvic viscera were easily exposed. There were no signs of adhesions about the appendages and the uterus, which was in its lower portion a mere shell, was carefully lifted up. The infundibulo-pelvic and round ligaments on either side were ligated and divided, the broad ligament separated and the ureters exposed without difficulty. It was remarkably easy to dissect the ureters out along the sides of the cervix and to ligate the uterine vessels above them. There seemed to be no carcinomatous involvement whatever about the ureters. The ureters were dissected free, and rolled well out to the lateral walls of the pelvis; the bladder was pushed far down on the vagina, and the utero-sacral ligaments divided well away from the uterus. Clamps were then applied and the parametria excised well out at the pelvic walls.

After sparging out the vagina and "walling off" with gauze on all sides, the Paquelin cautery was used to open the vagina anteriorly well below the growth. Thus the interior of the vagina was brought into view so that the cautery could be applied and the vagina amputated a full centimeter and a half below the margin of the growth on all sides, and the removal of the carcinomatous cervix and the uterus was most satisfactorily accomplished.

The patient was then returned to the ward in very good condition. Her convalescence was entirely uneventful and on Dec. 5, 1909, the following discharge note was made by Dr. Richardson: Abdominal incision, well healed; no tenderness.

*Pelvis.*—The vaginal vault is well closed over. There is considerable induration "high up" in the posterior vaginal wall. There are no definite nodules palpable although there is some irregularity in the thickening of the vaginal walls. No tenderness.

Since leaving the hospital, the patient has been entirely free from all symptoms and her physician writes, March 24, 1913 (almost three and one-half years since operation), Mrs. J. is apparently in perfect health. She has grown very stout and does a great deal of hard work.

Path. No. 14418. The cervix has been replaced by a cauliflower growth extending from a point well above the level of the internal os downward onto the vaginal mucosa especially posteriorly and to the left fornix, the excavations on either side having been formed by the previous curettage and cauterization. The exposed surface is seen to be covered by excrescences which have resulted from the actively proliferating carcinomatous cells since cauterization. The new growth is surrounded by a thin layer of fairly normal tissue, a wide margin of vaginal mucosa having been removed well below the carcinoma. The upper part of the body of the uterus is atrophic; its muscular walls present the usual appearance and the uterine cavity is lined with the characteristic senile endometrium. The tubes and ovaries are atrophic and show no adhesions.

In determining whether or not any particular case is, operable, many things are to be considered. In the first place the general condition of the patient is a very important factor on account of the extensive operation necessary and the usual

resulting surgical shock. Since carcinoma is a progressive disease a prolonged course of preparatory treatment is generally not justified, but in certain cases, especially those with little hæmoglobin, the general condition of the patient may be greatly improved by a short delay before operating. Obesity is not necessarily a contra-indication to the radical abdominal operation since, by the employment of the wide horizontal lipectomy described by Kelly, the depth of the field of operation may be greatly decreased, and, if ureteral catheters have been previously placed, the radical operation can be almost as readily completed as in patients of average size.

As regards the local condition, the mobility of the cervix and the new growth is generally considered the most important factor in determining whether or not the extensive operation is advisable. By a thorough microscopic study of the parametria, Kundrat,<sup>1</sup> in 1903, showed that the induration may be due to a secondary inflammatory condition rather than to a carcinomatous infiltration; hence the induration cannot be taken as an infallible sign to determine the operability. Decreased mobility of the cervix in cases of carcinoma of the uterus may be due to three causes, viz: (a) to direct extension of the new growth through the cervix into the broad ligament on either side; (b) to a secondary infection of the carcinomatous area with an inflammatory reaction in one or both broad ligaments; and (c) to an extensive pelvic peritonitis involving one or both broad ligaments. The differential diagnosis of these conditions is often very difficult and an exploratory operation is occasionally necessary to determine the extent of the new growth. Thus from the "Frauenklinik" of Leipsic, out of 221 apparently inoperable cases reported by Aulhorn,<sup>2</sup> 42 cases or about 20 per cent became apparently operable when the exploratory operation was done.

During the past year, an interesting case was reported by Dr. Bumm,<sup>3</sup> as follows:

A patient, 46 years old, suffering from atypical bleeding and pain since February, was admitted to his clinic in May, 1912. On pelvic examination, the cervix was found to be tumid and fixed; there was a large cavity containing broken-down masses, which, on the left side, was in direct continuity with the vagina and the parametrium. On rectal examination, it became evident that a voluminous infiltration extended from the cancerous mass going from the left, posteriorly, to the pelvic wall and rendering the cervix immobile. On account of the diffuse character of the infiltration, a removal of the cancer did not seem possible and the case was assigned to Roentgen treatment because of inoperability.

During June and July, the patient was treated at intervals of one to two days, according to the method described by Dr. Haendly<sup>4</sup> at the June Meeting of the Berlin Gynecological Society. In September, the treatment was resumed. About the middle of October on re-examining the patient, who up to that time had been receiving 800 Holzkecht [X-ray] units, equal to 1600 Kienböck, a marked improvement in the general and local condition was noted. The patient asserted that the bleeding had ceased entirely; that the discharge which had lost its putrescent odor, had diminished, and that the pain had disappeared. Instead of the former large crater-like cavity, there was now only a narrow cavity, in which the penetrating finger found no granulating masses. The cervix was hard and callous; the former diffuse infiltration toward the left side was transformed into a hard

tumor, which was quite separated from the pelvic wall and it and the cervix were now mobile. Operation now seemed possible and was done on October 22, 1912.

At the vaginal preparatory treatment, but little tissue could be scraped away with the sharp spoon, since it came into contact everywhere with a hard grating surface.

After opening the abdominal cavity, the peritoneum was found to be whitish and callous; the tubes and ovaries were agglutinated into one mass with the body of the uterus and could be liberated only with scissors.

The hardening was more marked in the tissues that were more exposed to the rays and it was necessary to liberate the left ureter with scissors from a white glistening callosity. The enucleation of the circumscribed cancerous nodule from the left parametrium was accomplished with ease; on both sides enlarged hard glands were removed from the trunks of the vessels. The convalescence was smooth.

From a clinical standpoint, the case described shows that by vaginal radiation large doses may be administered without causing burns of the mucous membrane; and that under the influence of intense X-rays a hardening of the tissues of the vaginal vault, the cervix and the pelvic connective tissue occurred which both hindered a further dissemination of the cancer and effected a purification of the cancerous crater and a cessation of ichor and hemorrhage. As a result of the sclerosis of the tissues, the diffuse infiltration of the parametrium became sharply circumscribed from the surrounding structures and the former inoperable cancer became operable.

While the sclerotic changes and the retrogression of the cancer dissemination could also be clearly seen and palpated in the sectioned specimen, the microscopic examination was somewhat disappointing. The lining of the cervical cavity showed everywhere a thin, not visibly changed layer of proliferating cancerous tissue, which was surrounded first by a thin layer of densely infiltrated tissue, and then by an extensive layer of sclerosed connective tissue which almost entirely superseded the muscle bands. In the parametrium and even outside the callous cancer nests of cells were found but the sclerotic glands were free.

A detailed description of this case is given on account of the very close similarity to our case. It is not uncommon to note a temporary relief in certain cases under X-ray treatment and occasionally an inoperable cancer becomes operable. One may ask, Why are the patients operated upon when improvement is evident? In answer to this question, one must determine upon what the improvement depends. Is it an actual improvement in which there is a "retrogression of the cancer-dissemination," or only an apparent retrogression due to a softening of the surrounding tissues which were the seat of a secondary infection? From a microscopic study of the pathological conditions, one is forced to conclude that the improvement is due to the disappearance of the inflammatory products which were primarily the cause of the induration. In Bumm's case, the microscopic examination showed that the cervical wound cavity was lined by a thin layer of proliferating, visibly unchanged cancerous cells although this layer was directly exposed to the strong X-rays at regular intervals for a period of over three months. Beyond this layer there yet remained a thin layer of densely infiltrated tissue and then a voluminous layer of sclerosed connective tissue. As seen from the accompanying illustration of the gross specimen of our case, although the cervical new-growth was extensively cauterized eleven days previously, there are numerous excrescences which on

microscopic examination show active cell proliferation. Photomicrograph I illustrates the extensive infiltration of the inflammatory products among the cancer cell-nests, while photomicrograph II shows an equally extensive inflammatory reaction surrounding the outlying cancer cells and muscle bundles.

Except for the coincident pelvic inflammatory disease in Bumm's case, the conditions were practically identical with those of our case. However, the single extensive cauterization apparently accomplished the same result as the prolonged X-ray treatment.

For many years the following method of cauterization of the cancerous area has been employed in this clinic.

The patient is placed in the perineal position and the usual cleansing done. A posterior retractor is then introduced into the vagina and the cervix grasped and drawn forcibly down by means of a tenaculum forceps. The greater part of the visible new growth is removed either by the fingers or a dull curet. The walls of the vagina are then protected by means of wet gauze pads which are held in position by anterior, posterior and lateral retractors and thus expose the cervix together with the carcinomatous growth on all sides. The cervical canal is thoroughly dilated to allow a more thorough cauterization and to determine whether or not a pyometra is present.

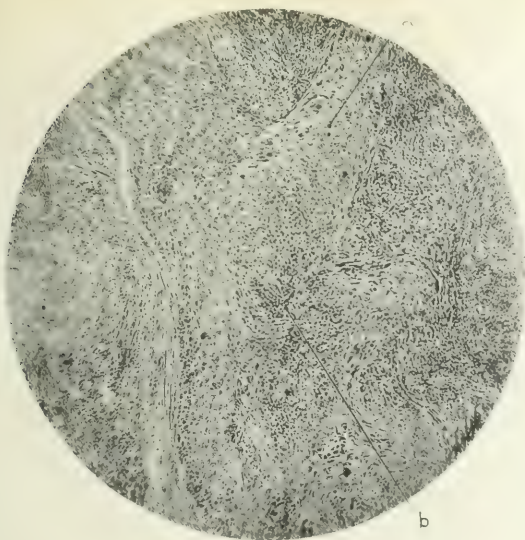
"Soldering irons," as recommended by Drs. William and Charles Mayo, which have been brought to a glowing heat, are then introduced directly into the cervical canal until the carcinomatous growth is thoroughly charred, care being taken not to burn too closely to the bladder and rectum. Occasionally the uterine vessels may be opened, thus giving rise to severe hemorrhage, necessitating their ligation, but as a rule the bleeding is completely controlled by the charring of the tissues. An iodoform gauze pack is then placed in the vagina and is allowed to remain in position for two to three days. This operation can readily be performed under gas anesthesia and with practically no shock to the patient.

During the interim between the preliminary operation and the radical abdominal extirpation, an effort should be made to improve the general condition of the patient. Practically all cases of carcinoma of the cervix of the uterus giving rise to symptoms are extensively infected, which renders the ultimate outcome of the operation much more serious; hence, any procedure tending to destroy the local infection is an important factor in the reduction of the percentage of primary mortality. The thorough cauterization should be supplemented by vaginal douches. The technique of disinfection of the vaginal field described recently by the authors<sup>1</sup> has proved very satisfactory; there has not been a single case of peritonitis following the radical abdominal operation where this method has been employed.

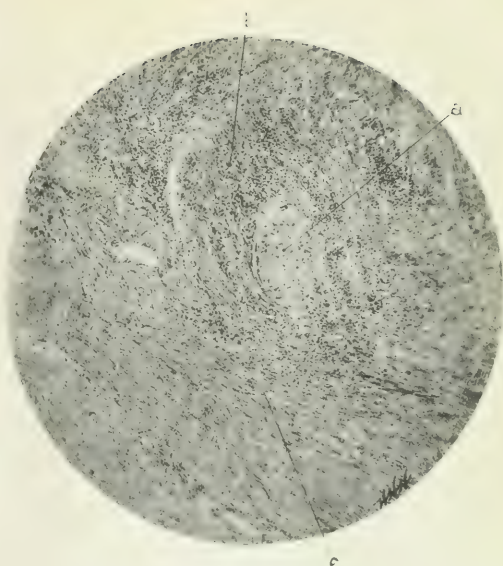
#### CONCLUSIONS

1. The extensive radical abdominal operation offers the greatest hope of absolute cure in patients suffering from carcinoma of the cervix of the uterus.
2. The percentage of operability has gradually increased with the adoption of the radical abdominal operation.





PHOTOMICROGRAPH I.—Showing carcinomatous area seen at *a* and extensive inflammatory infiltration at *b*.



PHOTOMICROGRAPH II.—Showing outlying cancer nest-cells, *a*, and very extensive inflammatory infiltration of the muscle bundles, *b*; the remaining cervical tissue surrounding the new growth is seen at *c*.



Squamous Cell Carcinoma of the Cervix.





3. An exploratory operation is occasionally necessary to determine whether or not the radical operation is to be attempted.

4. Pelvic induration may be due to the following causes: (a) to direct extension of the new growth through the cervix into the broad ligament on either side; (b) to a secondary inflammatory reaction in one or both broad ligaments; and (c) to an extensive pelvic peritonitis involving one or both broad ligaments. Hence the immobility of the cervix is not an infallible sign in determining whether or not a case is operable.

5. In advanced cases of carcinoma of the cervix a preliminary curettage and cauterization is advisable, for the following reasons:

(a) A large portion of the friable new growth may be removed through the vagina.

(b) It is an important procedure in the disinfection of the vaginal field.

(c) The induration in the broad ligaments, due to secondary inflammatory reaction, may be relieved, causing the new growth to become circumscribed and rendering a previously immobile cervix, mobile.

NOTE.—The authors are indebted to Mr. Max Brodel for the illustrations accompanying this paper.

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## TESTS FOR HEPATIC FUNCTION: CLINICAL USE OF THE CARBOHYDRATES.

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The discordant and inconclusive results of a series of sugar tests, made in the Medical Clinic of The Johns Hopkins Hospital, suggested that a careful analysis of the methods and results recorded in the prolific, but uncorrelated literature on the subject might throw some light on the clinical value of the carbohydrate tests. The results of this study seem to lead to conclusions quite different from the current ideas.

After a sketch of the literature, a consideration of the theoretical applicability of carbohydrates as tests for liver function, an account of the practical difficulties, and a criticism of the methods as used, an attempt will be made to correlate the findings of the various observers.

#### LITERATURE.

The discovery of the glycogenic function of the liver in 1857 by Claude Bernard immediately stimulated extensive work on carbohydrate metabolism, at first more by pathologists and physiologists, but subsequently by clinicians as well; it was during the course of a heated controversy which waged in the German and French literature, from 1875 to 1900, on the importance of the liver in effecting glycosuria after administration of large amounts of carbohydrates, that the idea of using the sugars as tests for hepatic disease first arose. Quincke,<sup>1</sup> v. Noorden,<sup>2</sup> Kraus and Ludwig,<sup>3</sup> Bloch,<sup>4</sup> and others, representing one side of the question, were unable to demonstrate any constant or marked reduction in sugar tolerance in cases of "liver disease," whereas the French school, especially Roger,<sup>5</sup> Baylac,<sup>6</sup> Bierens de Haen,<sup>7</sup> reported numerous instances of glycosuria after their tests, and championed the use of sugars in studying hepatic function.

The discrepancies in the results of these observers remained unreconciled until Strauss, in a series of papers published in

1898 and the years following, suggested that the use of different sugars in varying amounts probably gave the explanation. Following the technique of the German clinicians he administered<sup>8</sup> 100 gm. of grape sugar in 500 cc. of water on an empty stomach in a series of 38 *Leberkranken*, including carcinoma of the liver, cirrhosis, jaundice, gall-stones, and echinococcus; in only two cases was there a slight transitory glycosuria. In both of these, he remarks, there had been trauma in the liver region. Using, on the other hand, the test meal of the French school, which usually was 150 gm. of cane sugar, he also demonstrated in liver disease a proportion of glycosurias,<sup>9</sup> and felt, on the basis of his work with levulose, that it was this molecule of the cane sugar which was handled with difficulty. Strauss also criticised the interpretation of the reduction tests used in many of the previous observations, and concluded that glucose was particularly inapplicable, inasmuch as there was a mechanism apart from the liver which could handle this sugar. The latter view he supports by experiments of his own on liverless frogs, which he found could still tolerate considerable sugar; in fact, an amount only slightly below their normal tolerance.<sup>10</sup>

In 1901 Strauss<sup>11</sup> followed his sharp criticisms of the older tests by the introduction of levulose. Basing the rationale of his procedure on the work of Sachs,<sup>12</sup> who showed in many experiments that frogs whose livers had been removed had a lower tolerance for levulose than intact controls, a finding which could not be confirmed with dextrose, galactose, or arabinose, he studied a series of cases by the following technique: one hundred grams of levulose were given on an empty stomach, and urine voided during the four following hours was examined by Trommer's and Seliwanoff's tests, fermentation, and polarization. Of 25 cases of "liver disease" (*Leber-*

*kravitz*, cirrhosis 17, cancer 3, complete obstruction 4. "acute cholelithiasis with icterus" 1, amyloid 1, diabetes with cirrhosis 2, 28 or 90% showed an alimentary levulosuria, whereas of 58 individuals either healthy or suffering from ailments not involving the liver, only 6 or 10% put out sugar, and in the latter group he suggests "latent liver disease" as a possible explanation, inasmuch as they suffered from "obesity potiorum, gout, pneumonia, chronic fever, etc." There are no detailed tables, no clinical data, and no confirmation of the diagnoses.

Strauss' test rapidly became popular; the German *Wochenschrift* during the next ten years abound in brief reports on its application. Ferranini<sup>17</sup> tested 16 cases of "liver disease" by the Strauss method, and subsequently by administration of 100 gm. of grape sugar. His cases included 4 of atrophic cirrhosis, 1 of hypertrophic cirrhosis, 1 of liver lues, 1 "liver stasis icterus with cyst of head of pancreas," 1 of obstructive jaundice in lues, 1 of obstructive jaundice, 3 chronic malarias with enlarged livers, 1 liver cancer, 1 liver sarcoma (?), 1 tumor of left lobe of liver and of the mesentery and of the aorta (carcinoma?), 1 suppurating echinococcus cyst. He gives no details of the cases, nor any statements as to how the diagnoses were confirmed. In only 1 of these cases was it impossible to demonstrate sugar in the urine after levulose, whereas the glucose test was positive in 10 cases, in 7 of which only minimal amounts were demonstrable by Reals delicate test. He concludes that levulose is a better indication of liver insufficiency than glucose. Bruining<sup>18</sup> also obtained 90% of positive tests among 19 cirrhotics, 11 cases of catarrhal jaundice, and 1 carcinoma ventriculi et hepatis. Landsberg,<sup>19</sup> on the other hand, finds the test of no value after testing 21 cases of liver disease by Strauss' method, of which 9, or 45%, gave a positive test, as did 4 of 7 normals. He suggests as a fallacy that the tolerance varies in normal people. Chajes<sup>20</sup> supports Strauss, finding among 21 *nicht Leberkranken* 19 negative and 2 positive reactions to 100 gm. of levulose. Sabatowski,<sup>21</sup> from a study of 78 cases by Strauss' technique, concludes that cirrhosis, "moderate and severe grades," regularly gives alimentary levulosuria, that chronic passive congestion cases are negative as long as there is no serious destruction of liver substance, that infectious diseases at their height usually give a positive test, that in toxic jaundice there usually is a positive test, but that obstructive jaundice cases are negative unless there is a large destruction of liver. There are no statements as to how information about the extent of the anatomical lesions was obtained. V. Halasz<sup>22</sup> comments on the lack of clinical data in previous reports. Only 1 of 20 normal people put out levulose on 100 gm. Of 12 cirrhotics, 8 were positive; the remaining 4 "were incipient." The test was negative in "fatty liver," "hyperæmia and simple chronic atrophy," in 5 cases of secondary carcinoma, in 1 of catarrhal jaundice, and in 5 of obstructive jaundice. He felt that in doubtful cases a negative test was of value in excluding serious liver disease. Hohlweg<sup>23</sup> found 100 gm. of levulose not tolerated in 6 cases of stone in the common duct, 2 cases of cirrhosis, 1 case of catarrhal jaundice, and 100 gm. tolerated in 3 cases of stones

in the gall bladder, 2 cases of sarcoma of liver, 6 cases of secondary malignancy, and 10 cases of chronic passive congestion. Von Frey<sup>24</sup> considered as a positive test one in which 0.1 + gm. of levulose were put out after the administration of 100 gm., and on this basis found of 11 cirrhotics 7 positive, of 3 liver "tumors" none positive, of 4 cases of chronic passive congestion 2 positive, of 2 cases of icterus 1 positive, of 2 cases of hepatic lues 1 positive; 1 fatty liver positive, 1 catarrhal jaundice positive, 1 polycythemia negative. The diagnoses are unconfirmed. Churchman<sup>25</sup> found in 35 cases where the liver was clinically normal 9 positive and 29 negative; in 12 cases where the liver was clinically abnormal, 10 positive and 2 negative, whereas 2 cases clinically doubtful were both positive. He feels that neither a positive nor a negative test is conclusive. Falk and Saxl<sup>26</sup> summarized a large number of cases from the literature and from their own experience, emphasizing the relation between urobilinuria and levulosuria: of 351 cases 259 were positive and 72 negative. No details are given. Finally one should mention the communication of Schmidt,<sup>27</sup> who feels, on the basis of a series of acute febrile cases tested by Strauss' method, that the levulose (and urobilin tests) are of no value in liver disease accompanied by fever, inasmuch as they may be markedly positive without any liver lesions.

Bauer,<sup>28</sup> in 1906, introduced galactose as a liver test in a series of 10 cases of catarrhal jaundice, to whom he administered 40 gm. of galactose in 400-500 cc. of tea in the morning on an empty stomach, and determined quantitatively the amount of sugar put out during the following four to five hours. The cases were tested frequently during the course of the disease and it was found that galactosuria, at first marked, gradually diminished as the condition improved. In 1 case, at the height of the disease, 10 gm. (as much as 25%) was put out. In 12 cases of jaundice due to stones, on the other hand, the galactose output varied only slightly from the normal, the highest being 2 gm. In jaundice due to cancer, galactosuria was usually absent. He concludes that alimentary galactosuria is a constant symptom in catarrhal jaundice, whereas in other liver diseases except in some cases of cirrhosis, and in normals, it is not observed. Bondi and König<sup>29</sup> also found in 8 cases of catarrhal jaundice that, at the height of the disease, after 40 gm. of galactose, 2.0 to 5.9 gm. appeared, and as the patients improved only 0.4-1.8 gm. Falk and Saxl<sup>26</sup> quote 2 cases of cirrhosis. One put out 2.2 gm. on 40 of galactose, the other 0.5 gm. on 20 gm. V. Frey<sup>24</sup> gave 20 gm. of galactose to 8 *Leberkranken* and to 8 people with other diseases. He obtained 1 positive test in each group. Riess and Jehn<sup>30</sup> gave 40 gm. of galactose in a glass of carbonated water. They collected the urine in two 6-hour portions. They considered all cases pathological in which over 2 gm. were put out. On this basis, of 8 cases of gall stones 2 were positive; 5 cases of carcinoma were negative; of 5 cases of "ikterus lueticus" in the secondary period, in 3 the tolerance was not decreased, in 2 moderately so. In chronic passive congestion only 1 of 8 cases was positive. In 15 cases of cirrhosis the tolerance was normal in 9, 3 were on the border line, and in 3 there was a frank



galactosuria. In 17 cases of catarrhal jaundice only 1 mild case reacted normally. All the rest showed galactosuria. In other diseases the only positive result was in a case of croupous pneumonia. They think galactosuria speaks against cancer, chronic passive congestion, and uncomplicated gall stones. Normal tolerance speaks only against catarrhal jaundice. Finally Hirose<sup>22</sup> gave 25 gm. on an empty stomach, the patient already having been on a milk free diet. Of 23 cases 13 were negative, including lues, hepatitis, distomiasis, pseudocirrhosis, choledochus stenosis, icterus with fever, cancer of liver, and gall bladder. One chronic passive congestion was negative, 1 positive; 2 cholelithiasis cases were positive, 3 catarrhal jaundice positive, 4 cirrheses positive. One of the cirrheses put out 5 gm. In the other positive cases the outputs were all under 2 gm., in most under 0.5 gm. He agrees with Bauer that a positive result is more common in cirrhosis and catarrhal jaundice than otherwise, and that the more diffuse and severe the disease the easier alimentary galactosuria appears.

#### THEORETICAL APPLICABILITY OF CARBOHYDRATES AS TESTS FOR LIVER FUNCTION.

The newer views in regard to the liver as a center of the carbohydrate-regulating mechanism would seem to alter considerably the rationale of using the sugars as tests for hepatic function. As von Noorden<sup>20</sup> emphasizes, summarizing the results of studies on the glands of internal secretion, one must distinguish on the one hand disturbances in the formation of glycogen by the liver, and on the other disturbances in mobilization of the supply there stored. Cushing, Goetch, and Jacobson,<sup>21</sup> and also Weed, Cushing, and Jacobson,<sup>22</sup> have pointed out that certain lesions of the hypophysis, or of its autonomic nerve supply, are associated with glycogenolysis and glycosuria, whereas under other hypophysical conditions there is a greatly increased sugar tolerance. Similarly, it is known that the internal secretion of the pancreas exerts an inhibitory effect on the mobilization of glycogen by the liver, that the adrenals have an opposite accelerating effect, and that the thyroid less directly partakes in this sugar-regulating mechanism.<sup>23</sup> The studies of Eppinger and Hesse<sup>24</sup> on vagotonic and sympathicotonic states, indicate that the facility of glycogen mobilization varies also with the nervous control, and clinically Hirose<sup>25</sup> and Pollitzer<sup>26</sup> quote cases of "neuroses" with low sugar tolerance. It is clear then that disturbance in the fields of the internal secretions, and of the vegetative nervous system may result in a reduced or increased tolerance to carbohydrates without any essential lesion of the liver.

On the side of disturbances in formation of glycogen by the liver due to disease in that organ itself, the carbohydrates should theoretically be applicable as functional tests in so far, at least, as such disturbances might be accompanied by an alimentary glycosuria. The limits of physiological compensation, however, by uninjured liver tissue, or by regenerated cells, is not certain; possibly it may be quite adequate. Clinically, at least, one may see cases of cirrhosis where subsequently, at autopsy, the uninjured liver tissue is found to have undergone marked hyperplasia, compensation evidently

having been established until the final break. Furthermore, it is not clear to what extent other tissues may compensate for the liver when that organ is injured, at least in the disposal of carbohydrates. Experimental evidence<sup>27,28</sup> tends to show that some of the sugars, especially levulose and galactose, are handled almost specifically by the liver. Dextrose tolerance, on the other hand, is not reduced by producing Eck fistulas in dogs<sup>29</sup> and shunting the sugar into the general circulation. At any rate, while the matter is not finally settled, the possibility of compensation by other tissues for deficiencies in the glycogenic function of the liver is quite likely. Therefore, also with anatomical hepatic disease tolerance may be unaltered.

The theoretical basis, then, for the use of sugars as tests for hepatic function is definitely deficient.

#### PRACTICAL DIFFICULTIES OF CARBOHYDRATE TESTS.

Turning now to the actual application of the sugar tests, a series of practical difficulties immediately arises.

*Administration.*—Despite all precaution, in a certain number of cases a large dose of sugar sets up nausea, vomiting, or diarrhoea. It has been the experience that in the sicker patients, such as toxic cirrhosis or decompensated cardiac cases, untoward effects were the rule.

*Faulty Absorption.*—Many of the cases to be examined, particularly cirrhotics, patients with catarrhal jaundice, or with large livers due to chronic passive congestion, present disturbances in the mucosa of the gastro-intestinal tract which tend to render absorption sluggish and may interfere with all of the sugar entering the portal circulation. The presence of these abnormal gastro-intestinal conditions often leads, also, to a fermentation with breaking up of the sugar. The clinical evidence of this fact is ample in the cases where, after administration of sugar, there are frequent movements with great distention and passage of gas.

*Portal Obstruction.*—Here one encounters, perhaps, the most serious practical difficulty in applying the sugar tests, since it is met with in the most important group to be examined, namely: the cirrheses. In marked portal obstruction with well-developed collateral circulation, the material absorbed from the intestines does not reach the portal radicles alone, but in part enters the general venous circulation. Under these circumstances one has reproduced conditions similar to those which exist in the Eck fistula dog, where minimal amounts of sugar (levulose, galactose) may result in glycosuria.<sup>30</sup> It is clear, then, that the excretion of sugar in cases of cirrhosis gives no evidence of liver lesion.

*Retention of Sugars in Renal Disturbances.*—The work of Schlager and his associates<sup>31</sup> has demonstrated the retention of lactose in certain forms of nephropathy, and the same may hold true of other sugars, although none have been as carefully studied from this point of view. In cases of liver disease with renal complications, which are so common, this may introduce another source of error. Of importance also in this connection is the recent work of Rowntree, Fitz, and Gerachty,<sup>32</sup> showing that the slightest renal congestion causes lactose excretion.

*Variable Amounts of Carbohydrate in the Diet.*—In determining sugar tolerance on dogs it was found<sup>27</sup> that, to obtain reliable results, the animals must be on a carbohydrate free, or carbohydrate constant, diet, and that the sugar must not be administered oftener than every two days. An amount of sugar far below the tolerance fed on two successive days usually produced glycosuria, the animal being unable to handle a full dose, owing, perhaps, to the glycogen stored from the previous day. In patients, one has no idea of just how much sugar is stored at the time of the test. Hence it may happen that, with a normal liver, a comparatively small amount of sugar would produce glycosuria. The only manner of avoiding this complication would be by having the patient on a constant carbohydrate free diet for several days before the test, and this is unjustifiable in the majority of the cases to be tested.

#### CRITICISMS OF METHODS AS USED.

*Use of Arbitrary Amounts of Sugars.*—Landsberg<sup>28</sup> and Churchman<sup>29</sup> pointed out that the administration of an amount of sugar proportionate to body weight might be more satisfactory than the use of an arbitrary amount. Both, however, followed Strauss' original technique, and we have found no cases reported in which the dose was other than purely arbitrary. Thus, the Strauss method employs 100 gm. of levulose, Bauer<sup>30</sup> and Riess and Jehn<sup>31</sup> gave 40 gm. of galactose, whereas von Frey<sup>32</sup> gave 20 gm. of galactose.

To determine, if possible, just how great an error the use of arbitrary amounts of sugar might introduce, the tolerance of a series of dogs to lactose was determined as carefully as possible.<sup>33</sup> Animals were used rather than ward patients, inasmuch as the dosage and collection of specimens could be better controlled. In a series of sixteen observations on dogs weighing from 6 to 10.6 kilos the tolerance ranged from 1.35 gm. per kilo to 1.6 gm. per kilo, or from 7.5 to 16.5 gm.

In these animals, then, kept under constant identical conditions, and all apparently in good health, it appears that the absolute amount of sugar tolerated varied by more than as much as 100%, roughly in proportion to the body weight.

Now as experimental work<sup>34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100</sup> has shown that, apart from acute diffuse massive lesions, liver injuries are accompanied by only slight reductions in sugar tolerance (levulose, lactose, galactose), the threshold of excretion in the doubtful, less marked cases, where the test would naturally be applied, will lie only slightly below normal. Hence, in giving arbitrary amounts of sugar, such as 100 gm. of levulose, a diseased liver in a large man might be unaccompanied by glycosuria, whereas a healthy individual of small tolerance might excrete sugar.

The dogs referred to tolerated roughly 1.5 gm. lactose per kilo of body weight. The possibility naturally suggests itself of calculating the dose for an individual case on this basis. But, as Hofmeister<sup>34</sup> pointed out, the relation of tolerance relative to body weight holds only for animals in average health and in an average state of nutrition. Emaciation, obesity, edema, ascites, do not alter the tolerance proportionally to the change in weight which goes with such conditions. The patients to be examined, however, usually are either emaciated, dropsical, or edematous; hence one cannot calculate a true

normal tolerance from their weight, unless by estimation from their previous average weights or by calculations from height and weight tables. But, inasmuch as the reductions in tolerance in disease may be only slight ones, it seems that the only satisfactory method would be to determine directly the normal tolerance in the given individual, a procedure obviously impossible in one already diseased.

While some observers consider the putting out of any sugar after the test as a positive result indicating "hepatic insufficiency," others have assumed that at least a given amount or percentage must be excreted before the test should be counted as positive. In view of what has been said in the previous section, it seems that such a standard only serves still further to complicate the tests and render them more difficult of interpretation.

Finally, one must note that in applying the sugar tests no account has been taken of many of the sources of error mentioned; namely, portal obstruction, renal retention, intestinal fermentation and faulty absorption; nor were the patients on a constant carbohydrate diet.

#### DISCUSSION OF THE RESULTS OF THE CARBOHYDRATE TESTS.

Before attempting a comparison of the results of the various sugar tests it is necessary to make clear the exact purpose of the procedures. Is one looking for an index of a disease process in the liver, an anatomical lesion, or a temporary or permanent impairment of liver function? The conception of liver insufficiency is not a simple one; indeed from a clinical view-point such a condition is a rarity. Cases of advanced cirrhosis, with symptoms of general intoxication and showing at autopsy typical hepatic lesions, and some of the acute diffuse liver diseases, such as acute yellow atrophy, Weil's disease, etc., may perhaps be classed as hepatic insufficiencies (although even here the process is too general to ascribe it to one organ alone); but apart from these there are no clinical conditions where it is clear that the organism is suffering from impaired liver function. Even extreme hepatic lesions, such as the red atrophy of chronic passive congestion, luetic infiltrations, and malignant disease, do not present any symptoms which can be directly ascribed to hepatic insufficiency.

It is important to define, then, just what information one expects to gain from a positive sugar test. Throughout the literature confusion exists between "hepatic function" and "liver lesion." The excretion of sugar, according to the standards adopted by various writers, is invariably taken as indicating "hepatic insufficiency," a term which is invariably undefined. And yet, following the doctrine of factors of safety emphasized by Metzer, we know that one-half or more of an organ may be destroyed without interfering with the adequate performance of its function. It should be emphasized, then, that glycosuria after the administration of an amount of sugar which normally should be tolerated, means nothing more than a change in the function of metabolizing sugar. It is quite unjustifiable to take this as evidence of impairment of any other functions of the liver.

What evidence a properly conducted sugar test might offer for or against an anatomical lesion involving destruction of

more or less liver substance, it is hard to say. Theoretically there should be a reduction, but how far compensation by uninjured liver and by other tissues may prevent this is uncertain.

In spite of these theoretical objections, and in spite of the neglect by most writers of the important practical difficulties mentioned, a consideration of clinical reports shows a preponderance of positive tests in those cases classified as suffering from liver disease. The explanation lies, perhaps, in the difficulty of exact clinical diagnosis. In none of the earlier reports, and in only a few of the recent ones, are there adequate data to justify the diagnoses put down. We see, as examples of "liver disease," amyloid liver, diabetes with cirrhosis, "liver stasis with icterus," "fatty liver," "hyperamiamia and simple chronic atrophy," none confirmed by operation or autopsy. One writer states that of 12 cirrhotics, 8 gave a positive levulose test and 4 were negative. These four, he states, were "incipient." The positive clinical diagnosis of incipient cirrhosis is, of course, unjustifiable. In several of the earlier reports cases used as controls, but which gave a positive test, were thereupon regarded as suffering from latent liver disease, whereas in obviously diseased livers, with a negative test, compensation by remaining liver substance is resorted to in explanation. The constant finding of a positive galactose test in catarrhal jaundice by various writers seems suggestive, but one cannot reconcile the results of Bauer, using 40 gm., with those of Hirose, who used 25 gm., when the greatest output in Bauer's series was 10 gm. On this basis none of Hirose's cases should have excreted sugar at all.

The preponderance of so-called positive results becomes, then, less significant. When one considers the hopelessly inadequate data furnished in most of the reports, the inclusion in the list of positive cases of many where, in spite of some lesion, no essential disturbance in the liver exists—chronic malarias, hydatid cyst, etc., the inclusion of cases of portal obstruction in the positive reports—it does not seem fair to condemn or support the sugar tests on these statements.

The theoretical deficiencies of carbohydrates as tests for liver function, the use of arbitrary amounts of sugar, the lack of consideration of the disturbing factors, would seem to far outweigh the confused mass of case reports as evidence against the value of the sugar tests.

#### SUMMARY.

A consideration of the extrahepatic factors involved in the sugar regulating metabolism, the influence of the glands of internal secretion and of the vegetative nervous system, the ability of other tissues than the liver to handle sugar, and the ability of the uninjured liver substance to compensate in disease, make the sugars theoretically unsatisfactory as tests for hepatic insufficiency.

There are a series of great practical difficulties in applying the tests; namely, nausea, vomiting, and diarrhoea after feeding, faulty absorption, intestinal fermentation, portal obstruction with collateral circulation, retention of sugars in nephritis, and inconstancy in the diet.

There are serious objections to the methods as they have been applied; namely, the use of arbitrary amounts of sugar, and the use of a definite standard of excretion.

An analysis of the reports shows their significance to be lessened, owing to confusion in the conception of hepatic insufficiency, insufficient clinical data, and neglect of the practical considerations mentioned.

#### CONCLUSIONS.

1. Sugars are theoretically unsatisfactory as tests for liver insufficiency.
2. There are difficulties, which appear insurmountable, in the practical application of the tests.
3. The evidence from the clinical reports is not in such form as to prove or disprove the value of the tests.

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# TESTS FOR THE HEPATIC FUNCTION: LACTOSE TOLERANCE AS INFLUENCED BY THE LIVER NECROSIS OF CHLOROFORM POISONING.

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## INTRODUCTION.

In this study an attempt has been made to ascertain to what extent the tolerance for lactose or one of its split products, galactose, is reduced in experimentally produced liver lesions, and to determine whether such a reduction is an index of the degree of liver injury.

Experimental animals are especially favorable subjects for the study of this problem, since, in them, it is possible to control in a large measure the conditions of the metabolism experiment, and to find out the tolerance for a given carbohydrate in health before proceeding to establish the fluctuations in tolerance following liver injury. Although an endeavor was made to use the lactose test in a number of experimental liver lesions, we wish to report in detail only upon the results obtained with this test in liver necrosis produced by chloroform poisoning, and to refer briefly to the other experiments.

The use of chloroform to produce liver impairment and signs of liver insufficiency has many advantages over some of the other classical methods—liver extirpation, portal caval anastomosis, common bile duct ligation, and phosphorous poisoning—all of which have been employed to remove the liver partly or completely from participation in metabolism. It has been shown by Whipple and Sperry<sup>1</sup> that the essential injury of chloroform is in the liver tissue, and that this drug administered by inhalation to dogs for a period of one to two hours will invariably cause central liver necrosis. Moreover, the degree of this necrosis depends upon the duration of the anesthesia and upon the susceptibility of the animal. In general, the average amount of injury done to a dog's liver by two hours' chloroform anesthesia is a central necrosis involving about *two-fifths* of the parenchyma of each lobule.

These authors have shown further that from such an injury a liver can recover rapidly. At the end of the period of repair, which begins on the second or third day and is almost complete in six or seven days, the liver tissue regains its normal appearance by a rapid multiplication of the remaining liver cells. This process of repair is unattended by the formation of fibrous tissue.

By the use of chloroform, it is possible to produce an extensive injury in a short time and with a fair degree of certainty. For metabolism experiments, the production of liver injury by this drug has two additional advantages: First, the animal, if not fatally poisoned, will recover from the toxic symptoms in thirty-six to forty-eight hours after the anesthesia, thus permitting feeding tests to be carried on at a time when the liver necrosis is at its maximum; second, it is pos-

sible to study the return of the carbohydrate tolerance to normal after the liver has repaired the injury.

Our experiments seem to indicate that the tolerance for lactose in dogs may be reduced more than 50 per cent through the production of liver necrosis by chloroform anesthesia. It will be seen also that in non-susceptible animals in whom the injury is only slight, no such reduction in tolerance occurs, and that at the end of the reparatory activity of the liver an animal regains its normal tolerance for lactose. A reduction of the lactose tolerance, therefore, gives some information concerning the degree of liver injury, and this knowledge may prove of value in functional studies of liver disease.

## THE USE OF LACTOSE.

It was the original intention of the authors to use galactose for these experiments, since, according to Bauer<sup>2,3</sup> and other workers (Posselt,<sup>4</sup> Bondi and König,<sup>5</sup> Reiss and Jehn,<sup>6</sup> Hirose<sup>7</sup> and Wörner<sup>8</sup>), this monosaccharide has proved useful as a test for liver function. Because of the great cost of galactose, however, its use is impracticable in experimental work, and would be all the more so were it to be employed as a test in the clinic. Besides, there is sufficient experimental evidence to show that lactose can be used in the place of galactose in feeding experiments in which it is desired to determine the tolerance of the latter, provided suitable conditions exist within the intestinal tract for the cleavage of lactose into its constituent molecules—dextrose and galactose.

The work of Hofmeister,<sup>9</sup> Liezzatto,<sup>10</sup> and our own affords evidence that the reducing body, which appears in the urine of dogs following the administration *per os* of lactose in doses above the assimilation limit, is a monosaccharide whose properties are identical with those of galactose. This Hofmeister showed in two ways: First, following the ingestion of hydrolyzed milk sugar which consists of the molecules dextrose and galactose, dogs show a galactosuria; second, the tolerance of dogs for galactose is quantitatively one-half that for lactose.

Liezzatto<sup>10</sup> was able to confirm this observation. He fed lactose to dogs and subjected the reducing body which appeared in the urine to careful study: fermentation, polariscopic and galactosazone tests, as well as the chemical separation and identification of this carbohydrate. By all of these methods he demonstrated the reducing body to be galactose.

In our experiments, in order to exclude the possibility of a lactosuria, we supplemented the tests of Fehling and of Nylander with one described by Wohlk and also by Malfatti for the demonstration of lactose in the urine.

It has been assumed by those who have used galactose as a

test for liver function that after its absorption from the intestine this monosaccharide, like the others, is converted by the liver into glycogen. This assumption, however, has not been upheld by all workers. A study of the literature shows that only the more recent experimental studies afford evidence that galactose is a glycogen former. From their experiments Kulz<sup>11</sup> and Voit<sup>12</sup> and his school (Otto, Abbot, Lusk) concluded that the organism can form glycogen from dextrose and levulose. As for the other sugars, glycogen could be formed from them only if they were converted in the bowel into dextrose and levulose. This they did not believe to be true of lactose and galactose, which they found unchanged in the faeces.

The later experiments of Kausch and Socin,<sup>13</sup> Weinland,<sup>14</sup> Cremer,<sup>15</sup> and of Murschausen and Hoffmann<sup>16</sup> show that glycogen can be formed from galactose, but to a more limited extent and with greater difficulty than from the other monosaccharides. The discrepancy between these later results and those of the Voit school is due to the difference in the experimental animal used. As Weinland points out, pigeons, chickens, and adult rabbits differ from dogs, in that they lack the intestinal ferment lactase. The Voit school could not demonstrate an increase in glycogen after feeding lactose, because in the animals used by them the lactose was not split in the bowel into its constituent molecules—dextrose and galactose. Later work would seem to indicate, therefore, that feeding lactose to dogs increases the stored glycogen.

The difficulty of its assimilation probably explains the peculiar usefulness of galactose as a test for liver function. The position of this monosaccharide, lowest in the scale of carbohydrate tolerances, suggests that it differs from dextrose in that the bulk of the work of assimilating this molecule is done by the liver. That such is probably the case is shown by the work of Blumenthal.<sup>17</sup> This worker fed dogs the assimilation limit of a given carbohydrate and immediately after tested the power of the animal to handle the same carbohydrate when administered intravenously. He found that fifteen times as much dextrose as galactose could be injected before sugar was detected in the urine. This would seem to indicate that, apart from the liver, other tissues possess only one-fifteenth of the power to assimilate galactose as compared to dextrose. There is, however, no convincing experimental evidence that the liver is the only organ concerned in the conversion of galactose into glycogen, which, according to Sachs,<sup>18</sup> may be true for levulose.

#### METHODS.

Healthy dogs weighing from 6-10 kilos were used. The animals were kept in special metabolism cages. In such cages specimens of urine can be collected by placing containers beneath them. Before feedings, the cages were cleaned, thus insuring a minimum contamination of the urine.

It is important that the activity and diet of the animals be as nearly constant as possible during the experiment. These factors can be controlled by keeping the dogs in cages throughout an experiment, and by feeding them on a meat diet.

The animals were fed weighed amounts of sugar by stomach

tube, sufficient water being introduced through the tube to stimulate diuresis. The feedings were continued with varying amounts of sugar until the tolerance of the animal was determined. Animals should not be fed at too frequent intervals, so as to allow sufficient time for the utilization of the glycogen available from the previous feeding.

Specimens of urine were collected after the feedings. If the urine was contaminated by faeces or vomitus, the results were accepted only if they were negative. It is important to test the first specimen after the feeding, since it usually contains the sugar, if any be excreted. Before each feeding, a control specimen of urine was tested for the presence of sugar.

For the detection of sugar in the urine, the more common tests were used (Fehling, Nylander). In the earlier experiments, in order to exclude the possibility of a lactosuria, a test for the detection of lactose was also used.<sup>1</sup> No quantitative determinations were made.

#### DETERMINATION OF TOLERANCE.<sup>2</sup>

Before proceeding to determine whether an injury of the liver is associated with a reduction in the tolerance for a given carbohydrate, it is important to know the tolerance for that carbohydrate in health. In clinical cases of liver disease in which a carbohydrate test is done, no such preliminary knowledge is available. This has led to the adoption of arbitrary standards of normal tolerance. For instance, in the levulose test Strauss<sup>19</sup> adopts 100 gm. as a standard and in the galactose test Bauer<sup>1, c</sup> uses 40 gm.

The use of arbitrary standards of tolerance is open to criticism. It will be seen from Table II that the tolerance in grams varies as the body weight of the animal. In a state of health and under constant conditions of diet and activity this is approximately 1.5 gm. per kilogram of body weight. Hofmeister<sup>1, c</sup> has pointed out, however, that the estimation of tolerance in grams per kilogram of body weight is not accurate, since the animal varies in weight from time to time, according to its state of nutrition; a condition which should not influence its ability to handle carbohydrates.

This objection applies even more to the use of this method in determining tolerance in pathological states attended by emaciation, dropsy and ascites. For instance, in an experiment in which chronic passive congestion of the viscera and ascites were experimentally produced, the amount of lactose assimilated before and after the operation remained the same, although the animal had gained greatly in weight (11 lbs. to 20 lbs.), due to the accumulation of fluid in the abdominal cavity.

<sup>1</sup> This test, described by Wohlk and by Malfatti, is done as follows: 5 cc. of urine are made alkaline with about 2-5 cc. of strong ammonia and 5 drops potassium hydroxide are added. The mixture is then warmed in the water-bath. In the presence of lactose the solution turns red within five minutes. If dextrose be also present the solution turns reddish brown or brown. With this test the presence of 0.1 per cent lactose can be detected in the urine (Neubauer-Huppert, *Analyse des Harns*, 1910, I, 459).

<sup>2</sup> By tolerance we mean the largest amount of the sugar which can be fed without causing any to appear in the urine.

Again, the use in clinical cases of an absolute number of grams as a standard of normal tolerance, regardless of body weight, is also open to criticism. It will be noted in Table II that a dog weighing 6 kilograms may be able to assimilate 8-9 gm. as compared to 14-16 gm. for an animal weighing 10 kilograms. From a series of sixteen observations it was found that 10.5 gm. is an average of the normal tolerance. For a dog weighing 6 kilograms, this amount would far exceed the normal, whereas in one weighing 10 or more kilograms this arbitrary standard would fall below the actual tolerance.

In experimental work, where it is possible to establish an animal's normal tolerance preliminary to the production of a liver injury, both of the above objections fall away. Such information is of especial value where the extent of liver injury is small, for in such instances the difference between the assimilation limit in health and in disease may be so slight that the adoption of an arbitrary standard would be misleading. In clinical cases such preliminary tests are not available. The lack of these constitutes a great source of error in the clinical use of the carbohydrates as tests for liver function.

#### TOLERANCE OF NORMAL DOGS FOR LACTOSE.

Since the literature contains only a few incomplete observations on the normal lactose tolerance of dogs (cf. Table I) the authors have considered it well to tabulate the results of their findings. It will be seen from Table II that the tolerance of normal dogs for lactose is nearly constant (1.5 gm. per kilo)

TABLE I.—TOLERANCE OF NORMAL DOGS FOR LACTOSE AND GALACTOSE ACCORDING TO VARIOUS AUTHORS.

Author.	Lactose.		Galactose.	
	Grams.	Grams per kilo.	Grams.	Grams per kilo.
Hofmeister, <sup>1,c</sup> 1889.....	1-2	0.4-0.8	0.5-1	0.2-0.4
Liezzatto, <sup>1,c</sup> 1904.....	11	1.1	..	0.6
Quartas (Filippi), 1907..	...	1.54 males	...	...
		3.92 females		
Filippi, <sup>21</sup> 1907.....	10-15	0.8-1.0	...	...

TABLE II.—TOLERANCE OF NORMAL DOGS FOR LACTOSE.

No. of dog.	Sex.	Weight in kilos.	Tolerance in grams.	Grams per kilo.	No. of grams above (+) or below (-) tolerance 10.5 gms. standard.
12-90.....	F.	6.0	9.5	1.60	-1.0
12-89.....	F.	6.7	11.5	1.65	+1.0
12-80.....	F.	6.0	8.5	1.40	-2.0
12-76.....	F.	6.0	8.0	1.33	-2.5
12-73.....	F.	10.4	16.5	1.55	+6.0
12-58.....	F.	10.6	14.5	1.38	+4.0
12-2.....	F.	7.0	11.5	1.60	+1.0
12-14.....	F.	6.0	8.5	1.40	-2.0
12-54.....	F.	8.6	13.0	1.50	+2.5
12-38.....	F.	6.1	8.5	1.40	-2.0
12-3.....	M.	8.0	12.5	1.55	+2.0
12-121.....	F.	5.9	9.5	1.60	-1.0
R-1.....	F.	6.7	7.5	1.10	-3.0
R-11.....	F.	5.4	7.5	1.38	-3.0
R-111.....	F.	9.0	12.5	1.40	+2.0
12-122.....	F.	6.5	9.5	1.40	-1.0
Average			10.5	1.45	

when estimated in kilograms per body weight, but that wide variations exist in the absolute number of grams used. Our results agree very closely with those of Liezzatto<sup>1,c</sup> and of Quartas<sup>20</sup> for male dogs, but they do not confirm the finding of the latter that females will tolerate twice as much lactose as males.

#### LACTOSE TOLERANCE IN EXPERIMENTAL LIVER LESIONS.

Attention has been called to the advantages of using chloroform for the production of liver injury, and brief mention has been made of the reduced tolerance for lactose observed after chloroform poisoning. Before giving in more detail the results of these and other experiments, we wish to refer briefly to the observations of others in regard to the effect of experimental liver injuries upon the tolerance for carbohydrates.

Minkowski<sup>22</sup> (1886) was among the early investigators to study the effect of liver extirpation (in birds) upon metabolism. He found the tolerance for dextrose reduced.

Sachs<sup>1,c</sup> demonstrated that following liver extirpation in frogs the levulose tolerance is decreased, while that of dextrose, galactose and arabinose remains unchanged.

According to Filippi,<sup>1,c</sup> Eck fistula dogs can tolerate as much starch as normal dogs, but in them the tolerance for all sugars is reduced. Only one-half the amount of lactose and one-third the amount of levulose will be assimilated.

Hohlweg<sup>23</sup> (1909) and v. Frey<sup>24</sup> (1911) each demonstrated reduced tolerance for levulose in rabbits, both after phosphorus poisoning and after ligation of the common bile duct.

Roubitschek<sup>25</sup> (1912) and Wörner<sup>1,c</sup> (1913) showed that phosphorus poisoning in rabbits causes a reduction in the galactose tolerance. The former fed galactose and the latter injected it into the portal vein, so as to do away with the possibility of faulty intestinal absorption.

Reiss and Jehn<sup>1,c</sup> (1912) found that the galactose tolerance in dogs is not lowered after ligation of the common bile duct. They point out that in dogs ligation of the duct does not produce any liver injury unless the pancreas also be injured (Fischer, *Deut. Arch. f. klin. Med.* 1910, C, 329; *ibid.*, 1911, CIII, 157).

#### ECK FISTULA.

The clinical symptoms of an Eck fistula dog suggest that weeks after the operation, when the dog is in good health and well nourished, the animal is not suffering from any marked degree of hepatic insufficiency. It is known (Voegtlin and Bernheim, Whipple and Sperry) that the liver in the early stages does undergo slow atrophy with some fatty degeneration as a result of the scanty blood supply. It is not unlikely that the return of the functional activity of such a liver to normal after a longer period is due to the remarkable reserve capacity of the liver, aided by the establishment of a collateral circulation.

In two experiments with Eck fistula dogs, the lactose tolerance was found reduced to about one-half the normal. This agrees with the observation of Filippi. There is a fallacy,



however, in concluding that the reduced tolerance for lactose is the result of liver injury. One cannot exclude the possibility that only a part of the sugar reached the liver by way of the hepatic arteries and that the remainder made its way into the systemic circulation and was excreted by the kidneys.

The experiments are cited rather to emphasize a point already made, namely, that the galactose molecule is in large part handled by the liver. It will be noted from the protocols and the Tables III and IV that in both animals the tolerance for dextrose remained high even after the production of the fistula, whereas that of lactose was reduced one-half. This would seem to indicate that other tissues were still assimilating the dextrose molecule well, whereas the assimilability of the galactose fraction of the lactose was reduced, as would be expected, in proportion to the amount of liver tissue removed from the general metabolism by the portal caval anastomosis.

Dog 12-2.—Black and tan mongrel, female, 15½ lbs. (7 kilos).

Jan. 25. Lactose 10.5 gm. Urine negative for sugar.

Jan. 29. Lactose 12 gm. Urine clear. Sugar positive. Tolerance 11 gm. lactose.

Feb. 1. Operation.—Ether anæsthesia. Portal caval anastomosis.

Feb. 2. Animal is in good condition.

Feb. 10. A. m., lactose 7 gm. Urine positive for sugar.

Feb. 13. Urine negative for sugar (control). Lactose 6 gm. Urine positive for sugar.

March 10. Lactose 4 gm. (63 per cent reduction). Urine negative for sugar.

March 12. 9.30 a. m., galactose 3 gm. 4 p. m., urine clear. Sugar positive.

March 16. Galactose 2 gm. Urine positive for sugar. Tolerance of galactose less than one-half that of lactose.

March 20. Dextrose 20 gm. Urine negative for sugar.

April 2. Phenoltetrachlorphthalein excretion 17 per cent.

As the animal's condition improved this excretion gradually rose, reaching 40 per cent on June 18 (Dr. Whipple). Thus it would appear that the hepatic function, as indicated by the lowered phthalein output (35-50 per cent for normal dogs), was actually diminished about the same time when the lactose tolerance was reduced to one-half.

TABLE III.—Dog 12-2.

Sugar.	Date.	Sugar in grams.	Grams per kilo.	Sugar in urine.	Remarks.
Lactose	Jan. 25	10.5	1.5	+	Tolerance 11 gm. (1.5 per kilo). Good recovery. 36% reduction. 45% reduction. 63% reduction. Tolerance 5 gm. (0.7 per kilo).
	Jan. 29	12.0	1.7	+	
	Feb. 1	*			
	Feb. 10	7	1.0	+	
	Feb. 13	6	0.85	+	
	March 10	4	0.57	0	
Galactose	March 12	3	0.42	+	Tolerance 2 gm. (0.3 per kilo).
	March 13	2	0.28	+	
	March 16	2	0.28	+	
Dextrose	March 20	20	2.8	0	Tolerance below 20 gm.

\* Operation: Eck fistula.

Dog 61.—Fox terrier, female, 13 lbs. (6 kilos).

March 12, 1912. Operation.—Portal vein ligated.

Nov. 25, 1913. Animal is healthy and active. Lactose 6 gm. Urine clear. Sugar positive. No diarrhoea.

Nov. 27. Lactose 3 gm. (0.5 gm. per kilo). Urine obtained 6 hours later is clear and negative for sugar. Estimated tolerance 4.5 gm. Lactose (0.8 gm. per kilo).

Dec. 2. Galactose 3 gm. Urine clear. Sugar positive.

Dec. 3. Galactose 2 gm. Urine clear. Sugar negative. Tolerance 2.5 gm. galactose (0.4 gm. per kilo).

Dec. 4. Dextrose 9 gm. Urine negative for sugar.

Dec. 5, 6, 7, 8. Dextrose 12, 15, 18, and 24 gm. successively. Urine in each case negative for sugar. Tolerance for dextrose above 24 gm.

April 5. Phenoltetrachlorphthalein excretion 45 per cent (Dr. Whipple).

It would appear that at this time the functional capacity of the liver as indicated by this test had nearly reached normal.

TABLE IV.—Dog 61.

Sugar.	Date.	Weight in grams.	Grams per kilo.	Sugar in urine.	Remarks.
Lactose	Nov. 25	6	1.0	+	Tolerance 4.5 gm. (0.5 per kilo).
	Nov. 27	3	0.5	0	
Galactose	Dec. 2	3	0.5	+	Tolerance 2.5 gm. (0.4 per kilo).
	Dec. 3	2	0.33	0	
Dextrose	Dec. 4	9	1.5	0	Tolerance above 24 gm.
	Dec. 6	12	2.0	0	
	Dec. 7	18	3.0	0	
	Dec. 8	24	4.0	0	

## CHLOROFORM POISONING.

## METHOD.

The normal tolerance of an animal was determined by the method already described. Chloroform anæsthesia was then administered for a period of about two hours. About 36-40 hours after the anæsthesia the animal was fed by stomach tube an amount of lactose which was below the normal tolerance. The urine voided after this feeding was tested for sugar. Before each feeding the urine was tested to make certain that it was sugar free.

In order to correlate the knowledge gained of the functional activity of the liver from the lactose test with the amount of injury done, a piece of liver tissue for microscopical section was removed under ether anæsthesia and with aseptic precautions. The animal was then allowed to repair the liver injury for a period of a week or ten days and the experiment was repeated with a larger or smaller reduction in the quantity of lactose, depending upon the results of the previous test.

## EXPERIMENTS.

In one instance an experiment as described above was done four times upon the same animal. The observations upon this animal (dog 12-121) will be summarized, since they are complete and are like most of the others. This dog, a healthy female, was found to have a tolerance of 9.5 gm. lactose. After a 2½ hours anæsthesia the animal was quite ill and the urine the next morning contained a little sugar, which disappeared

on the evening of the same day. This is one of the few instances in which sugar was found in the urine after chloroform anaesthesia (meat diet). About forty hours after the anaesthesia the dog was fed 6½ gm. lactose, which represented a reduction of 33 per cent of its normal tolerance. On this amount, sugar appeared in the first voiding about seven hours later.

The animal was tested again a week after the first anaesthesia. It was found that coincident with the repair of the liver injury the lactose tolerance had returned to normal. Chloroform anaesthesia was then administered for 1½ hours, an interval of forty hours was allowed to elapse and 6.4 gm. lactose were administered. Again the animal excreted sugar in the urine. A piece of liver removed about ten hours after the test feeding showed a central necrosis involving one-fifth to one-third of each lobule. Nine days later the experiment was repeated with a 50 per cent reduction of the lactose, and finally after a similar interval a fourth test was done with a 60 per cent reduction. After the 50 per cent reduction sugar appeared in the urine, but failed to appear after the 60 per cent reduction.

It may be assumed from the liver tissue removed after the second anaesthesia, that in this particular animal the administration of two hours chloroform by inhalation was sufficient to produce a liver necrosis involving one-fifth to one-third of the parenchyma of each lobule, and that at least this amount of liver injury was present in Experiment C when a 50 per cent reduction was still attended by the presence of sugar in the urine.

This experiment in connection with some of the others cited below makes it fairly certain that following a chloroform anaesthesia of two hours the tolerance for lactose may be reduced at least 50 per cent. The reduction of the functional activity as indicated by the lactose test corresponds fairly closely to the degree of injury demonstrable microscopically.

Dog 12-121.—Brown, female, fox terrier, 13 lbs. (5.9 kilos).

*Experiment A.*—May 30. A. m., lactose 9 gm. P. m., urine clear, negative for sugar. No vomiting or diarrhoea.

June 1. 10 a. m., lactose 10 gm. 3.30 p. m., urine clear; sugar positive. Tolerance 9.5 gm. lactose.

June 9. 2-4.30 p. m., chloroform anaesthesia 2½ hours; 1¼ ounces; well taken.

June 10. Animal looks ill; purulent conjunctivitis of both eyes; slight jaundice; does not eat. A. m., urine gives atypical reaction for sugar. 10 p. m., urine (control) negative for sugar.

June 11. 10 a. m., lactose 6.5 gm. (33 per cent reduction of tolerance). 5 p. m., urine clear; sugar positive. Second voiding negative for sugar.

*Experiment B.*—June 16. 3 p. m., weight 10 lbs. Lactose 8 gm. P. m., clear urine; sugar negative.

June 18. A. m., lactose 9 gm. Urine clear; sugar positive. Tolerance 8.5 gm. lactose.

June 21. 4 p. m., chloroform anaesthesia 1½ hours; 1 ounce; poorly taken. Vomited at end of anaesthesia.

June 22. Animal looks dull; vomits; does not eat.

June 23. 9.30 a. m., urine clear. Negative for sugar (control). Lactose 6.4 gm. (25 per cent reduction). 5 p. m., urine clear, positive for sugar.

*Operation.*—8.30 p. m., ether anaesthesia. Incision made through the right rectus; liver was exposed and wedge-shaped piece re-

moved and placed in formalin for histological study. Cut surfaces of liver tissue were approximated by ligature.

*Liver.*—Microscopical section. Repair of first injury not complete. Central necrosis involving one-fifth to one-third of each liver lobule. Middle zone shows rather diffuse, fatty degeneration. Mitotic figures are very numerous.

June 25-30. Animal more active; eats well; is evidently repairing injury. Stitches removed; wound healed.

*Experiment C.*—July 5. Animal has recovered completely. Chloroform anaesthesia 2 hours; 1 ounce. Vomited at end of anaesthesia.

July 6. A. m., dog looks ill; does not eat. Urine negative for sugar.

July 7. 10 a. m., dog a little more active. Urine (control) negative for sugar. Lactose 4.2 gm. (50 per cent reduction). 4 p. m., urine positive for sugar. 9 p. m., urine still positive for sugar.

*Experiment D.*—July 15. A. m., lactose 7 gm. P. m., urine clear, negative for sugar. Tolerance has evidently risen to normal.

July 17. Chloroform anaesthesia 2 hours; 1¼ ounces. Vomited.

July 19. A. m., urine (control) negative for sugar. Lactose 3 gm. (64 per cent reduction). P. m., urine clear; negative for sugar.

TABLE V.—DOG 12-121.

Date.	Chloroform.	Lactose in gm.	Sugar in urine.	Remarks.
EXPERIMENT A.				
May 30..	....	9	0	
June 1...	....	10	+	Tolerance 9.5 gm.
June 9... 2½ hrs.	....	....	0	No post anaesthetic glycosuria.
June 11..	....	6.5	+	Control negative; 33% reduction of tolerance.
EXPERIMENT B.				
June 16..	....	8	0	Period of repair one week.
June 18..	....	9	+	Tolerance 8.5 gm.
June 21.. 1½ hrs.	....	....	0	No post anaesthetic glycosuria.
June 23..	....	6.4	+	25% reduction of tolerance. Operation. Control 0.
EXPERIMENT C.				
July 5...	2 hrs.	....	0	Period of repair two weeks.
July 7...	....	4.2	+	50% reduction of tolerance.
EXPERIMENT D.				
July 15..	....	7	0	Period of repair 10 days.
July 17.. 2 hrs.	....	....	0	No post anaesthetic glycosuria.
July 19..	....	3	0	64% reduction of tolerance. Control 0.

Dog R-I.—Brown, female hound, 14½ lbs. (6.7 kilos).

*Experiment A.*—June 23. 9.30 a. m., lactose 9 gm.; 5.30 p. m., urine positive for sugar.

June 25. 9.30 a. m., lactose 8 gm. P. m., urine clear. Sugar positive.

June 28. 9.30 a. m., lactose 7 gm. P. m., clear urine; negative for sugar. Tolerance 7.5 gm. lactose.

July 5. Chloroform anaesthesia 2 hours; 1 ounce; well taken.

July 6. A. m., animal drowsy; but not extremely ill. Slight

jaundice of sclerae and mucous membranes. No vomiting. Urine (control) negative for sugar.

July 7. 10 a. m., lactose 4.5 gm. (40 per cent reduction). 4 p. m., urine, clear specimen; sugar positive. 9 p. m., next voiding, sugar negative.

Operation.—9 p. m., piece of liver tissue removed for study. Wound very moist; considerable oozing.<sup>3</sup>

Liver.—Microscopic section. Central necrosis involving three-fifths of the cells of the liver lobule. There is a very thin middle zone of fatty degeneration. About the portal areas, nearly one-third of the parenchyma is pretty normal.

July 9. Animal in good condition; wound is healing.

Experiment B.—July 15. Lactose 7 gm. P. m., urine negative for sugar. Tolerance evidently risen to normal.

July 17. Chloroform anesthesia 2 hours;  $\frac{3}{4}$  ounce.

July 19. Animal dull; does not eat. Urine (control) negative for sugar. 10 a. m., lactose 3 gm. (60 per cent reduction). 4 p. m., urine negative.

TABLE VI.—Dog R-I.

Date.	Chloroform.	Lactose in gm.	Sugar in urine.	Remarks.
EXPERIMENT A.				
June 23..	....	9	+	
June 25..	....	8	+	
June 28..	....	7	0	Tolerance 7.5 gm.
July 5... 2 hrs.	....	....	0	No post anæsthetic glycosuria.
July 7... ..	....	4.5	+	40% reduction of tolerance. Operation. Control 0.
EXPERIMENT B.				
July 15..	....	7	0	Period of repair 8 days.
July 17.. 2 hrs.	....	....	0	No post anæsthetic glycosuria.
July 19..	....	3	0	60% reduction of tolerance. Control 0.

Dog R-II.—Spotted, white female hound, 12 lbs. (5.4 kilos).

Experiment A.—July 10. A. m., lactose 7 gm. P. m., urine clear. Sugar negative.

July 12. A. m., lactose 8 gm. P. m., urine clear. Sugar positive. Tolerance 7.5 gm. lactose.

July 14. Chloroform anesthesia 2 hours;  $\frac{3}{4}$  ounce; well taken.

July 15. Animal dull. A. m., urine shows presence of sugar. P. m., sugar absent in second voiding.

July 16. Lactose 3.5 gm. (50 per cent reduction). P. m., urine clear; positive for sugar.

Operation.—8.30 p. m., piece of liver tissue removed in usual way.

Liver.—Microscopic section. Central necrosis involving about three-fifths of each liver lobule; practically no fatty zone. Marginal parenchyma shows a little diffuse, fatty degeneration with fine fat droplets in the protoplasm. Mitotic figures visible.

July 18. Animal more active.

Experiment B.—July 21. Animal is evidently repairing injury. Lactose 6.5 gm. P. m., urine clear and negative for sugar. Tolerance is rising to normal.

July 22. Chloroform anesthesia 2 hours; 1 ounce; well taken.

July 23. Dog dull; vomited. Urine negative for sugar.

<sup>3</sup> It has been shown by Whipple and Hurwitz (J. Exp. M., 1911, XIII, 136) that the hemorrhages of chloroform poisoning are due to inefficient coagulation resulting from a decrease in the fibrinogen of the blood.

July 25. A. m., lactose 2.5 gm. (65 per cent reduction). P. m., urine clear. Sugar positive.

TABLE VII.—Dog R-II.

Date.	Chloroform.	Lactose in gm.	Sugar in urine.	Remarks.
EXPERIMENT A.				
July 10..	....	7	0	
July 12..	....	8	+	Tolerance 7.5 gm.
July 14.. 2 hrs.	....	....	+	Sugar present in first voiding after anesthesia.
July 16..	....	3.5	+	50% reduction in tolerance. Operation. Control 0.
EXPERIMENT B.				
July 21..	....	6.5	0	Period of repair one week.
July 22.. 2 hrs.	....	....	0	No post anæsthetic glycosuria.
July 25..	....	2.5	+	65% reduction of tolerance. Control 0.

This animal (Dog R-II), it appears, was particularly susceptible to chloroform poisoning; a two-hour anesthesia producing a central necrosis involving three-fifths of each liver lobule. At this time the animal excreted sugar, although the quantity of lactose administered was only one-half its normal tolerance. On a second occasion, and with probably the same extent of liver injury, this dog put out sugar in the urine after a 65 per cent reduction of the quantity assimilated in health.

Dog R-III.—Spotted, white, female hound, 20 lbs. (9 kilos).

Experiment A.—July 10. 10 a. m., lactose 12 gm. P. m., urine clear; sugar negative.

July 12. Lactose 13 gm. P. m., urine clear; positive for sugar. Tolerance 12.5 gm. lactose.

July 14. Chloroform anesthesia 2 hours;  $\frac{3}{4}$  ounce; well taken.

July 15. Dog looks active. Urine: Specimens a. m. and p. m., both negative for sugar (control).

July 16. Lactose 5 gm. (60 per cent reduction). P. m., urine gives reaction for sugar.

Operation.—9 p. m., piece of liver removed in usual way.

Liver.—Microscopic section. Lobules show central necrosis involving one-half to three-fifths of the liver cells. There is a thin middle zone of fatty degeneration. About one-fifth of each lobule is practically normal.

TABLE VIII.—Dog R-III.

Date.	Chloroform.	Lactose in gm.	Sugar in urine.	Remarks.
EXPERIMENT A.				
July 10..	....	12	0	
July 12..	....	13	+	Tolerance 12.5 gm.
July 14.. 2 hrs.	....	....	0	No post anæsthetic glycosuria.
July 16..	....	5	+	60% reduction of tolerance. Operation. Control 0.
EXPERIMENT B.				
July 21..	....	11.5	0	Period of repair one week.
July 22.. 2 hrs.	....	....	0	No post anæsthetic glycosuria.
July 24..	....	5	+	60% reduction of tolerance. Control 0.



*Experiment B.*—July 21. Dog is quite active; evidently is repairing injury. A. m., lactose 11.5 gm. P. m., urine negative for sugar. Tolerance rising to normal.

July 22. *Chloroform anesthesia 2 hours; one ounce.*

July 23. Animal drowsy; does not eat; vomited.

July 24. Urine (control) negative for sugar. A. m., lactose 5 gm. (60 per cent reduction). P. m., urine gives sugar reaction.

In this experiment (Dog R-III) the observations were repeated twice under exactly the same conditions with the same results. In the first instance, and probably also in the second, a two-hour anesthesia caused a central necrosis involving one-half to three-fifths of the liver cells. At this time the functional activity of the liver was probably low, as was indicated by the presence of sugar in the urine following the administration of only 60 per cent of the amount of lactose which the animal tolerated before the anesthesia.

Dog 73.—Black and white mongrel, female, 23 lbs. (10.4 kilos).

Feb. 19. 9.30 a. m., lactose 15 gm. P. m., urine: Sugar negative.

Feb. 24. Lactose 16 gm. Urine: Sugar negative.

Feb. 25. 10.30 a. m., lactose 17 gm. P. m., urine clear. Sugar positive. Tolerance 16.5 gm. lactose. Repeated Feb. 28, with same result.

March 6. *Chloroform anesthesia 2 hours; 1 ounce; well taken.*

March 7. Dog is dull; vomited.

March 8. Animal still ill. Urine (control) negative for sugar. 9.30 a. m., lactose 15.5 gm. (7 per cent reduction). 5 p. m., specimen of clear urine is positive for sugar; lactose test negative. Urine from next voiding negative for sugar.

*Operation.*—8 p. m., ether anesthesia. Piece of liver removed in the usual way. Wound is moist, and there is considerable oozing.

*Liver.*—Microscopical section. Central necrosis involving from two-fifths to one-half of the liver lobule. There is a middle zone of fatty degeneration. Mitotic figures are numerous.

Dog 12-38.—Small yellow mongrel, female, 13½ lbs. (6.1 kilos).

*Experiment A.*—Dec. 23. Lactose 12 gm. Urine clear. Sugar positive.

Dec. 27. Lactose 11 gm. Urine clear. Sugar positive. No diarrhoea.

Jan. 5. Lactose 9 gm. Urine positive for sugar.

Jan. 11. Lactose 8 gm. Urine negative for sugar. Tolerance 8.5 gm. lactose.

Jan. 14. *Chloroform anesthesia 1½ hours.*

Jan. 15. Animal in good condition. Urine negative for sugar.

Jan. 16. Lactose 7 gm. (17 per cent reduction). Urine negative for sugar.

Jan. 22. *Chloroform anesthesia 2¾ hours; 2¼ ounces; not well taken.*

Jan. 24. Dog dull A. m., lactose 7 gm. Urine, catheterized specimen positive for sugar. No sugar in voidings during same day.

*Operation.*—Piece of liver removed in usual way.

*Liver.*—Microscopical section. Repair is not complete. Injury involves about central one-third of each lobule. Middle zone shows pronounced fatty degeneration involving one-fifth of the lobule. Wandering cells everywhere numerous.

*Experiment B.*—Feb. 6. Animal seems well; injury is evidently repaired. A. m., lactose 7 gm. Urine negative for sugar. Normal tolerance returning.

Feb. 17. *Chloroform anesthesia 2¼ hours; 1½ ounces.*

Feb. 19. A. m., lactose 7 gm. Urine positive for sugar.

This animal (Dog 12-38) showed some resistance to chloroform poisoning. After a 1½ hours' anesthesia no sugar appeared in the urine, even though the normal tolerance was reduced only 17 per

cent. A week later, however, an anesthesia of 2¼ hours did result in a liver necrosis involving one-third of each lobule.\* Now the administration of the same amount of lactose was attended by the appearance of sugar in the urine. A repetition of this experiment about two weeks later gave the same result.

Dog 12-30.—Fox terrier, male. 19.8 lbs. (9 kilos).

Dec. 6. Lactose 18 gm. Urine shows the presence of sugar; but reaction is only slight. Tolerance estimated at 17 gm. lactose.

Dec. 8. *Chloroform anesthesia 1½ hours; ¾ ounce.*

Dec. 9. Animal looks fairly active; has not vomited. Urine clear; negative for sugar (control).

Dec. 10. A. m., lactose 11 gm. (35 per cent reduction). P. m., large quantity of clear urine. Sugar negative.

Dec. 11. *Chloroform anesthesia 1 hour; ½ ounce.*

Dec. 12. Animal does not look ill. Urine negative for sugar (control).

Dec. 13. A. m., lactose 11 gm. (35 per cent reduction). P. m., specimen of clear urine shows no sugar.

*Operation.*—8 p. m., piece of liver tissue removed in usual way.

*Liver.*—Microscopical section. Repair of previous injury is almost perfect. There is no definite necrosis, and little central fatty degeneration.

Dog 12-27.—Fox terrier, female, 24 lbs. (11 kilos).

Nov. 29. Lactose 25 gm. Urine positive for sugar.

Nov. 30. Lactose 22 gm. Urine positive for sugar.

Dec. 2. Lactose 17 gm. Urine negative for sugar. Estimated tolerance 19 gm. lactose.

Dec. 5, 6, 7, and 8. Glucose 22, 27, 33, and 44 gms. given successively without producing a glycosuria. Tolerance for glucose 44 gm. plus.

Dec. 8. 9.30 p. m., *chloroform anesthesia 1 hour; ½ ounce.*

Dec. 9. Dog in good condition. Urine positive for sugar—post anesthetic (?). 9 p. m., urine negative for sugar (control).

Dec. 10. Lactose 13 gm. (31 per cent reduction). Urine several hours later clear and negative for sugar.

Dec. 11. 3.30 p. m., *chloroform anesthesia 1 hour; 1 ounce.*

Dec. 12. Animal looks drowsy. Urine negative for sugar (control).

Dec. 13. 12 m., lactose 13 gm. (31 per cent reduction). Diarrhoea.

Dog 12-3.—Bull terrier, male, 16 lbs. (7.3 kilos).

Dec. 3. Lactose 11 gm. Urine clear. Sugar positive. No diarrhoea.

Dec. 5. Lactose 15 gm. Urine contaminated.

Jan. 25. Lactose 13 gm. Urine clear; faint reduction to Fehling's solution. Tolerance 12 gm.

Feb. 3. *Chloroform anesthesia 3 hours.*

Feb. 5. Lactose 11.5 gm. (11 per cent reduction). Urine clear. Sugar negative.

Dogs 12-30, 12-27, and 12-3 also showed some resistance to chloroform poisoning.

In dog 12-30 a 1½ hour anesthesia did not produce sufficient liver injury to lower the lactose tolerance 35 per cent. An additional anesthesia of one hour administered two days later did not produce any appreciable necrosis, and a lactose test showed that the tolerance was not reduced.

\*The only slight injury observed in this and other animals following an anesthesia of such duration is due to the repetition of the anesthesia before the liver injury resulting from the first was complete. It is known that during repair the liver is resistant to chloroform poisoning.

TABLE IX.—SUMMARY OF CHLOROFORM EXPERIMENTS.

Number of dog.	Normal tolerance.	Duration of anesthesia.	Sugar in urine.	Reduction of tolerance.	Per cent reduction.	Extent of liver injury.
12-73.....	16.5	2 hrs.	+	1.5	7	$\frac{1}{2}$ to $\frac{1}{4}$ lobule
12-3.....	13.0	3 hrs.	0	1.5	11	.....
12-38.....	8.5	1 $\frac{1}{2}$ hrs.	0	1.5	17	.....
.....	8.5	2 $\frac{1}{2}$ hrs.	+	1.5	17	$\frac{1}{4}$ of lobule
12-38 B.....	8.5	2 $\frac{1}{2}$ hrs.	+	1.5	17	.....
12-27.....	19.0	1 hr.	0	6.0	31	.....
12-30.....	17.0	1 $\frac{1}{2}$ hrs.	0	6.0	35	.....
.....	17.0	1 hr.	0	6.0	35	No necrosis
12-121 A.....	9.5	2 $\frac{1}{2}$ hrs.	+	3.0	33	.....
12-121 B.....	8.5	1 $\frac{1}{2}$ hrs.	+	2.0	25	$\frac{1}{4}$ to $\frac{1}{2}$ lobule
12-121 C.....	8.5	2 hrs.	+	4.3	50	.....
12-121 D.....	8.5	2 hrs.	0	5.5	64	.....
R <sub>1</sub> -A.....	7.5	2 hrs.	+	3.0	40	$\frac{1}{2}$ lobule
R <sub>1</sub> -B.....	7.5	2 hrs.	0	4.5	60	.....
R <sub>2</sub> -A.....	7.5	2 hrs.	+	3.5	50	$\frac{1}{2}$ lobule
R <sub>2</sub> -B.....	7.5	2 hrs.	+	5.0	65	.....
R <sub>3</sub> -A.....	12.5	2 hrs.	+	7.5	60	$\frac{1}{2}$ to $\frac{1}{4}$ lobule
R <sub>3</sub> -B.....	12.5	2 hrs.	+	7.5	60	.....

## OTHER LIVER LESIONS.

Experiments were made to determine whether the lactose tolerance was reduced after phosphorus poisoning and after ligation of the common bile duct. These observations are not complete and no definite conclusions can be drawn from them.

The following experiment (dog 12-44) is of interest because of the application of this test to an animal in which experimental passive congestion had been successfully produced.

Dog 12-44.—Irish poodle, female, 13 lbs. (5.9 kilos).

Jan. 19. 10 a. m., lactose 8 gm. Urine negative for sugar.

Jan. 20. 9 a. m., lactose 9 gm. Urine faintly positive for sugar. Tolerance 8.5 gm. lactose.

Jan. 21. Operation.—(Dr. McClure): Stitches placed in inferior vena cava just above diaphragm; lumen narrowed to 2-3 mm. in diameter.

Jan. 23. Animal made good recovery from operation. Wound is healing. Lactose 8 gm. Urine negative for sugar.

Jan. 31. Marked generalized edema of tissues of back, legs and abdominal walls; abdomen swollen and tense. Weight 19 $\frac{1}{4}$  pounds.

Feb. 1, 4, 6, and 7. Repeated abdominal tapplings. More than 5 litres of ascitic fluid removed.

Feb. 10. Lactose 9 gm. Urine positive for sugar.

Feb. 13. Lactose 7.5 gm. Urine negative for sugar. Tolerance continues within normal limits after a period of hepatic congestion lasting about three weeks.

April. During this month the functional activity of the liver as estimated by the phenoltetrachlorophthalein output in the faeces continued slightly below normal, it being 30 and 40 per cent (Dr. Whipple).

Autopsy.—After a period of six months the liver showed typical passive congestion with central atrophy and fatty degeneration.

In this animal the established normal tolerance before operation was 8.5 gm. lactose. Two days after the operation (cf. protocol) the animal was given 8 gm. lactose without excreting sugar. About three weeks after the operation and after a series of tapplings, 7.5 gm. lactose (0.5 gm. below the normal tolerance) were fed without causing the appearance of sugar in the urine. It would appear, therefore, that in this animal the presence of chronic passive congestion of the liver was not associated with a reduction in the lactose tolerance.

## CONCLUSIONS.

1. There is experimental evidence to show that in the intestinal tract of dogs lactose is split into its constituent molecules—dextrose and galactose—and that after feeding lactose to dogs, galactose is excreted in the urine.

2. Studies by various workers show that when lactose is split, the liver can form glycogen from galactose, but to a more limited extent and with greater difficulty than from the other monosaccharides.

3. The experiments cited show that it is more accurate to determine the tolerance of an animal before producing a liver injury than to accept arbitrary standards of normal tolerance, expressed either in total number of grams or in grams per kilogram of body weight.

4. Whereas the normal tolerance of dogs for lactose expressed in grams per kilogram of body weight is fairly constant, the total number of grams tolerated by different animals shows wide variations.

5. Eck fistula dogs show a reduced tolerance for lactose, which, however, may result from flooding of the systemic circulation with sugar rather than from liver injury.

6. In susceptible animals, central necrosis produced by chloroform poisoning results in the reduction of the lactose tolerance by 50 per cent or more.

7. In one animal with chronic passive congestion of the liver, no reduction in the lactose tolerance could be demonstrated.

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## PROCEEDINGS OF SOCIETIES.

## THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

April 17, 1913.

On the Importance of Bacteriemia in the Diagnosis of Sinus Thrombosis of Otitic Origin. A Clinical and Bacteriological Study. E. LEBMAN, M. D., New York.

A brief abstract follows:

In the course of bacteriological studies of the blood (now numbering over 4700) of infections of various kinds, observations were made by us in cases of otitic infection which we believe to be of great importance from a diagnostic and therapeutic standpoint. The first publication of our results was made in the form of a discussion before the American Otolological Society in June, 1906. Further observations made by Dr. Celler and the writer were reported at the meeting of the Association of American Physicians in 1909, and an exhaustive account of our results was presented last year before the International Otolological Congress.

Dr. Celler and the writer studied 277 cases of otitis media and found that streptococci were present alone or with other organisms in 189 cases (81.46 per cent); *Streptococcus mucosus* occurred 20 times (10.3 per cent), and the pneumococcus 19 times (8.2 per cent). The organisms next most commonly found were the staphylococcus, *Bacillus pyocyaneus* and *Bacillus proteus*. Mixed infections were not uncommon. Although the pneumococcus is found in a comparatively large number of cases of otitis media, there are but few undoubted records of sinus thrombosis due to this organism. Until the time of reading this paper we had seen no case of sinus thrombosis surely due to the pneumococcus, but since then we have met one case with an atypical pneumococcus in the blood.

We have made blood cultures in 149 cases of otitis media and mastoid disease uncomplicated by sinus thrombosis and meningitis. Some were complicated by epidural and brain abscess. In all these cases the blood cultures were negative.

Our method consists in withdrawing ten to twenty-five cubic centimeters of blood from a vein (usually from an arm) and incubating this in a number of media, which are observed for five days. In children, and particularly infants, we are often compelled to use smaller amounts. Our studies in infants and in children under the age of six years is not extensive enough to warrant deductions. A couple of experiences make us believe that bacteriemia in children can arise more easily than in adults from uncomplicated otitis media or mastoid disease.

Anaerobic methods were used occasionally. The method introduced by Duel and Wright, of New York, was also tried and gave no different results from our own method. Microscopical studies of the blood were made by Drs. Fried and Sophian, but the results are not sufficient to warrant advising the method.

Our positive results in blood cultures in cases of otitis media were obtained only in those complicated by meningitis or sinus thrombosis (including bulb thrombosis). There

were six streptococcal meningeal infections; bacteriemia occurred in two. In three cases of pneumococcus meningitis the organism was found in the blood in one. In eight cases of meningitis due to *Streptococcus mucosus*, the cocci were were found in the blood in six.

In 43 cases of sinus thrombosis we obtained positive results in 34 (80 per cent); streptococci in 30 (90 per cent); *Streptococcus mucosus* in 3 (8.8 per cent); *Bacillus proteus*, once. We believe that nearly all cases of sinus thrombosis (except the aseptic type) are accompanied by bacteriemia at some time or other.

The possible causes of negative results in blood cultures of cases of sinus thrombosis are the following:

1. The organisms may be so few in number that none are obtained in the amount of blood used.

2. Anaerobic organisms may be missed by not making use of a proper technique.

3. Cultures may be made before the organisms are present in the blood.

4. The cultures may be made after there are no more bacteria discharged from the local focus. This may be due to two reasons:

- a. Organization.

- b. The thrombus may break down, but instead of separate bacteria, pieces may enter the circulation and cause metastatic infections. Or if individual bacteria are also thrown into the circulation, they may be killed off, while those in the bits of thrombus are protected from the bactericidal power of the blood. In either event, one would have a case of metastatic infection (pyemia) without bacteriemia.

5. The bacteriemia may be intermittent.

6. The bactericidal power of the blood of the patient may be normally so marked or develop to such an extent that the bacteria are very rapidly killed off.

7. The end or ends of the clot may be bacteria-free even though the central part is infected.

8. The thrombus may be infective, but it may close the vessel in such a fashion that no bacteria are carried into the circulation.

9. The thrombus may have originally been bacteria-free or have become so.

As a result of our earlier studies, we claimed that cases in which streptococci are found in the blood after the mastoid has been operated upon (and in which clinical symptoms persist) are cases of sinus thrombosis. One must exclude all other possible primary foci. According to our late studies even those cases which before operation showed a bacteriemia, and in which other causes for the bacteriemia and meningitis could be excluded, proved to be cases of sinus thrombosis.

While there is a certain amount of evidence in the literature that a general infection can occasionally occur from the middle ear without sinus thrombosis being present, and while some of the literature on experimental investigations (much of which must be accepted with reserve) points the same



way, it is best that in any given case in which organisms are found, that the surgeon take for granted that the sinus is involved. He can then deal with the case according to the clinical condition of the patient at the time that the report is made. We recently had a case under observation in which we obtained a positive blood culture from the patient, but the symptoms were so mild that we desisted from advising operation. The temperature persisted for several days and the patient made a complete recovery. While this case may have been one in which spontaneous organization of a thrombus occurred (since spontaneous organization is not as uncommon as is generally believed), it is also possible that it is one of the exceptional cases in which a general infection occurred without a thrombus being present.

When present, the bacteria were usually found by means of blood culture, within twenty-four hours after the blood was obtained. The number of bacteria varied from one in several cubic centimeters of blood up to two hundred and forty-five per cubic centimeter of blood. They usually disappeared very promptly after operation upon the sinus and ligation of the jugular vein (sometimes in one or two hours). In the few cases in which they persisted in the blood, notwithstanding ligation of the jugular vein, there was usually found an extension of the thrombus to the other side or involvement of the bulb or an acute (ulcerative) endocarditis (this occurred in only one case), or a meningitis or a thrombosis of the jugular vein below the point of ligation.

The most valuable field for the blood culture studies has been in the cases in the border line between otitis and other diseases. In the publication made in the Transactions of the International Otological Congress for 1912 will be found a complete description of all cases in which blood cultures were found positive, and a study of these will show how remarkably valuable these investigations have been in clearing up doubtful cases.

The negative blood cultures also have a value. Absence of bacteria from the blood in a doubtful case would make one careful not to explore for a thrombus until the possibility of an intercurrent disease had been excluded or until symptoms had become so severe as to justify an exploratory procedure. If blood cultures should be negative in a given case and the symptoms persist, whether there is present a sinus thrombosis or not, acute (ulcerative) endocarditis can be excluded. In such cases it is advisable to take two cultures. A negative blood culture is also useful to prove that the general infection has been stopped, after ligation of the jugular vein has been performed.

As stated above, it is important to exclude all other possible primary sources of infection. There is not sufficient time to discuss all these; common ones are the following: Infections arising in the veins, lungs, bones, gall-bladder, appendix, kidneys, intestines, and male and female genito-urinary tracts. A number of forms of infection are particularly important to keep in mind, because they come into play so often in connection with cases of otitic infection. They are tonsillar infections, acute (ulcerative) endocarditis, accessory sinus

infections, nasal infections, scarlet fever, typhoid fever, pneumonia and erysipelas. Accessory sinus infections seem to cause a general infection only when they are very severe. In scarlet fever there seems always to be a primary focus which is the point of origin of the streptococemia. Fulminating cases of scarlet fever show no bacteriemia. In erysipelas, streptococemia is very rare except in fatal or complicated cases.

When our paper was published in 1909, there was a certain amount of opposition to our views, particularly by Drs. Duel and Wright, of New York, who found general infection quite frequent in uncomplicated cases of otitis media and mastoiditis. A recent report by Page, from the same institution, gives results that entirely confirm our own. Similar results have also been found in the New York Eye and Ear Infirmary by Dr. Dixon and Dr. Hays.

#### DISCUSSION.

DR. H. O. REIK: As an otologist I believe I agree with Dr. Libman in practically all of his conclusions. To the otologist the value of the method will lie in the amount of aid and assistance it affords in making an early diagnosis of sinus thrombosis. In the past we have had to rely for diagnosis mainly upon the characteristic fluctuations of temperature noted in this disease, but the delay incident to such observations causes loss of much valuable time and, perhaps, of many lives that might be saved by earlier surgical intervention. Six years ago, during the Congress of Physicians and Surgeons, I read a paper before the American Otological Society presenting a résumé of the cases of lateral sinus thrombosis reported by members in the Transactions of that association from the time it was organized, and there were some striking features bearing upon the importance of early diagnosis and proper methods of operation.

Dr. Libman has remarked that sinus thrombosis may get well without operation. There is no question about that, for there are a number of cases reported where the diagnosis would appear to be almost certain and yet the patients got well without operation upon the vessel. Nevertheless, in spite of these clinical records and of the experimental evidence of organization, recanalization and so forth, it is equally true that lateral sinus thrombosis, if left untreated or if treated without surgical assistance, has a very high mortality, almost 100 per cent. Even with direct operation upon the sinus, the mortality is high, about 60 per cent, when the sinus is opened and the thrombus attacked without preliminary ligation of the internal jugular vein. If the vein be first ligated and the diseased portion of the sinus then treated, the mortality drops to 25 per cent, or thereabouts. I mention these findings because of what Dr. Libman said about inspection of the supposedly diseased sinus as a means of diagnosis. I want to emphasize the fact that the otologist cannot by this means, except occasionally, make a positive diagnosis and that he can never say there is not a thrombus present. There may be a parietal or even a complete thrombus without visible signs on the external surface of the vessel. Furthermore, in

any method of palpation of the sinus or of puncturing that vessel to secure material for examination you take additional risk of disseminating infection. If lateral sinus thrombosis is suspected the sinus may be exposed and prepared for incision, but should not be touched until after ligation of the jugular; having placed a barrier in the way of extension, by tying off the vein, one may deal with the sinus without fear of inducing further trouble.

However, looking into the future, I would say that if we are to save a larger proportion of these infections of the lateral sinus we must endeavor to recognize the beginning of the attack upon the sinus by the otitic disease. These cases practically all begin with a phlebitis of the sinus wall, a clot begins to form on the inner wall of the vessel, becomes infected, and, with breaking down, causes dissemination of poison through the vascular system. It must be made possible for us to recognize and diagnose the stage of inflammation of the vessel wall, the phlebitis, that we may operate before the thrombus is organized, or, at least, before it becomes a focus of infection.

Now, Dr. Libman made an exception to some of his conclusions regarding thrombosis of the sinus in children and I want to say that possibly the reasons for this exception are more apparent than real. We must not forget that this affection in children has probably been often overlooked, because the infection is prone to occur in a different position from that of the adult. McKernon has shown that in young children the infection happens frequently, but that it occurs in the portion called the bulb of the jugular vein rather than in the sigmoid curve, as is general in adults. That is, in adults the disease attacks the upper part of the sinus from the mastoid cells, while in the child it reaches the vessel through the floor of the tympanic cavity.

DR. LIBMAN: I have seen about 30 cases of pyelephlebitis. In only one of them did I succeed in getting a positive blood culture; it is interesting to note that in that case the foramen ovale was open. The fact that bacteria are not generally found in the blood current in pyelephlebitis is a very interesting one, and I have made the same observation that Dr. Thayer has made, that one can use this fact in helping to establish the diagnosis in certain cases in which one is in doubt as to whether there is an acute or subacute bacterial endocarditis or a suppurative pyelephlebitis.

The bacteria are probably not found in the blood in the cases of pyelephlebitis, because the pieces which are dislodged from the portal vein are caught in the liver and produce local infections there. It is, furthermore, of interest to note that whenever one gets an infection in any part of the body in which there is an abundance of carbohydrate, one is not apt to see a general infection develop. This not only holds true of infections of the liver, but is particularly of interest in connection with infections of the lactating breast. I cannot remember having seen a case of general infection arising from suppurative in the lactating breast, no matter how severe the clinical picture was. It must be an unusual occurrence. I might also express here my surprise at the comparative in-

frequency of general infections in diabetics, notwithstanding the frequency of local infections in them.

I have stated these facts because they have impressed themselves upon me in the course of my studies. How far they will be affected by further experience I do not know.

There is one point I would like to bring out, and that is concerning the question about ligating the jugular vein before operating upon the sinus. If one is at all sure that a sinus thrombosis is present, it is better to ligate. In one case which I have seen, in which the jugular vein was not ligated before the sinus was operated upon, there was a marked increase in the number of bacteria in the blood following the operative procedure. This patient developed an acute bacterial endocarditis (malignant endocarditis). Of course, one cannot claim that the endocarditis would not have developed anyhow, but it certainly would have been better to have avoided throwing more bacteria into the blood current than had been present before. Every once in a while we see a case on the operating table that goes into collapse, and in some of these cases I believe the collapse is due to dislodging of bits of thrombus from the sinus. If the operator is not certain that a sinus thrombosis is present, he might explore the sinus, and as soon as he sees evidence that a thrombus is present, perform the jugular operation and then go back and attack the sinus.

It is not to be forgotten that there are some reports in the literature of cases of spontaneous recovery from sinus thrombosis without operation. A number of observers have described cases of organization and canalization of thrombi in the lateral sinus in cases in which no operation whatsoever was done upon the sinus. My general impression is that this is more apt to occur in children than in adults.

*April 21, 1913.*

**Exhibition of a Case of Chorio-epithelioma.** DR. J. WHITRIDGE WILLIAMS.

#### DISCUSSION.

DR. CULLEN: Last year I reported before the Society a case of hydatidiform mole with bilateral multiple corpora lutea cysts.

The patient (Mrs. H. B. S.), was 20 years old. Her last menstrual period had occurred on Nov. 19, 1911. On Dec. 15 she noticed a small drop of blood. On Feb. 3 she had a fall and went to bed. On the night of the fall she had a chill and commenced having pains in her abdomen. On Feb. 6th discharge of blood and water was noted and her family physician, Dr. George Hocking, then examined her and said she was threatened with a miscarriage. From Feb. 6th up to March 9th, when I saw her, there had been a discharge of blood each day. On Feb. 28th there was some swelling of the feet and the following day her face began to swell.

On March 10th the uterus was dilated and numerous hydatid cysts came away. On March 23d the patient was doing remarkably well, but masses were still present posterior to the uterus, just above the cul-de-sac.

On opening the abdomen we found bilateral multilocular ovarian cysts, each about  $8 \times 5 \times 4$  cm. They lay beneath the uterus, which was twice its natural size. On account of the age of the patient I hesitated to remove both ovaries completely; I therefore resected them, saving a small portion at the hilum of each ovary. When the operation was completed the ovary on either side of the uterus was about half its natural size. Each of the multilocular cysts contained clear fluid, and was evidently a corpora lutea cyst.

A month ago I learned from Dr. Hocking that this patient had become pregnant, but a few weeks before term she had had a fall and consequently the child was born dead.

This case demonstrates what we can sometimes do by conservative operations. There was evidently sufficient ovary left on either side to provide for a subsequent pregnancy.

Histological examination of the cysts showed that they were all corpora lutea cysts.

The possible coexistence of these multilocular cysts with hydatid mole should always be thought of, as in some instances the thickening on either side of the uterus has led the surgeon to believe that the uterus contained a malignant growth and that the lateral thickening was due to an extension of the supposed chorio-epithelioma to the broad ligaments.

Three years ago we had a very interesting inoperable case of chorio-epithelioma in Ward H. (Gyn. No. 18034; Path. No. 16776). Each Bartholin's gland was over 1 cm. in diameter and on being squeezed the contents escaped as a small ribbon similar to that from a tube of tooth paste. This tissue on microscopic examination proved to consist of typical chorio-epithelioma. Pathologists experience great difficulty in differentiating histologically between simple hydatid mole and chorio-epithelioma. As a rule the diagnosis can be definitely made only when a portion of the uterine wall has been invaded or when metastases exist. The clinical picture is of the greatest importance in determining whether or no malignancy exists.

Dr. Williams was particularly fortunate in his diagnosis of this condition from scrapings and in the substantiation of his opinion by the findings in the uterus after its removal.

**Plague.** DR. RICHARD P. STRONG.

#### DISCUSSION.

DR. CHAS. W. YOUNG: *Mr. Chairman:* I don't suppose this meeting realizes the great amount of information that Dr. Strong has brought to us this evening. Dr. Strong, by his investigations in Manchuria, has added very much to our knowledge of the pneumonic plague. While others were referring to their past work, he was out in the field doing something, and in the International Plague Conference Dr. Strong was able to bring evidence as to what he had found out. He has not discussed his previous and very interesting work on immunity in *bubonic* plague. There is a point about the mask of which he has spoken. It was perhaps useful in Mukden, but at Harbin the temperature reached 35 or 40 degrees below zero. You can realize that when one went out in such a tempera-

ture the mask became covered with a coating of ice and the air did not go through the mask, so there was little protection from it. If goggles were used it was extremely difficult to see on account of the condensation on the lenses. In examining patients in the open air I believe that the goggles can be dispensed with. There is always a bacteremia in pneumonic plague. In five cases cultures were positive, four of them in living patients and one in a cadaver of a patient recently dead so there is a bacteremia at least in the later stages of the disease.

Dr. Strong has spoken of autopsies he performed. These twenty-five necropsies are more than all the previous discriptions of pneumonic plague had been based on. He performed the first autopsies that have ever been performed in China with official cognizance.

May 19, 1913.

**Multiple Congenital Osteochondromata, etc.** DR. T. R. BOGGS.

#### DISCUSSION.

DR. BLOODGOOD: The case reported and illustrated by Dr. Boggs is one of great interest and extreme rarity.

I have been interested in lesions of bone for many years, and while I have seen many examples of single bone lesions, multiple lesions are very infrequent.

There is no doubt that in Dr. Boggs' case there are multiple exostoses. These are visible and palpable without the aid of the X-rays, but, in addition, there seem to be changes in the marrow cavity of some of the bones. These changes are most marked in the tibia, humerus and upper end of the femur. Unfortunately in this case there has been no opportunity as yet, either by operation or autopsy, for examination of either the exostoses or of the bone marrow. In addition, this case shows other defects in the osseous system, especially bending of bone as shown in the radius, humerus and necks of the femora. Up to this time, in the literature I know of no case of multiple exostoses in which the bone marrow has been examined either at operation or autopsy. Dr. Boggs' patient also exhibits congenital defects in the nervous system and in the muscles. From my reading of the literature and limited experience, I am inclined to view this case as an example of congenital multiple exostoses. These exostoses may be bone, or cartilage, or both. The defect begins perhaps in early embryonic life and is in the development of the osseous system. We have as yet no proof that the bone changes depend upon any of the ductless glands, such as the thyroid or pituitary body. These patients at birth and in young childhood may exhibit no signs of the exostoses, but later in life, especially during puberty, growth in one or more of the exostoses may take place, giving rise to visible and palpable tumors with or without pressure symptoms.

Dr. Dunlop of Washington sent me X-ray studies of the father and three sons—all exhibiting multiple congenital exostoses, but none of these patients suffered from the bone lesion.



In a recent article by Paul Frangenheim (*Beitr. z. klin. Chir.*, 1911, LXXIII, 226), read since I discussed Dr. Boggs' paper, I find that in an autopsy investigation in a case of multiple cartilage exostoses changes were also found in the marrow cavity—cartilage formations.

As a rule we have observed in diseases of bone similar pathological processes occurring in a single bone and in many bones. I was especially interested in this phase of the question in an investigation on benign bone cysts, giant-cell sarcoma and bone aneurysms (*Transactions of the Amer. Surg. Assn.*, 1910; *Annals of Surgery*, August, 1910). I was able then to collect from the literature examples of cyst formation in the following diseases of the skeleton: Ostitis fibrosa (von Recklinghausen's disease), 12 cases; ostitis deformans (Paget's disease), 5 cases; osteomalacia, 6 cases; cysts in multiple enchondromas, 2 cases; in multiple sarcoma, 1 case; and in multiple bone lesions of mercurial poisoning, 1 case. In multiple myeloma I was unable to find any recorded case of cyst formation, nor in the cases of multiple carcinoma metastases to bone, nor in multiple exostoses of the congenital type. The full literature is given in my article.

Of all these lesions of the skeleton the enchondroma and exostosis are the only examples of bone defects of congenital origin. It is also interesting to note that in these two lesions no examples of malignant degeneration have been observed. We also do not know why in some cases of multiple congenital exostoses the tumors remain quiescent, in others they grow at different periods of life after puberty, giving rise to all grades of deformity and discomfort.

Dr. Boggs' patient is an example of the most exaggerated form of this condition. It would be very interesting to know, if we could be able to prevent the later development of these serious changes of a congenital lesion, which, as a rule, in early life gives rise to no discomfort or deformity.

There is no doubt that the development of bone depends upon a normal thyroid and pituitary gland, and we now know also that serious joint and osseous lesions may be produced by poisons, such as mercury, as well by toxins, such as from the intestinal tract. The presence of Bence-Jones bodies has not been found in these cases of multiple exostoses. It usually occurs in the multiple myeloma and now and then in metastatic carcinoma. Dr. Boggs, I think, has also reported an example of the latter.

I hope that Dr. Boggs will be able in his case to have an opportunity for careful investigation of the chemistry and histology of the bone lesion.

**DR. BOGGS:** In reply to Dr. Bloodgood's inquiry about autopsies I would say there have been some, but a very few. A few exostoses have shown cystic degeneration, but for the most part the descriptions of these tumors is like that of normal bone. I have found no reference to any changes in the marrow.

**Report of Cases.** DR. T. S. CULLEN.

#### DISCUSSION.

**DR. BLOODGOOD:** The cases reported by Dr. Cullen and the one by Dr. Boggs bring out the interesting fact that we know very little of the etiological factors in most tumors, either benign or malignant. We are quite familiar with many congenital tumors—exostoses, lipomas, pigmented moles, naevi, fibromyxomas of nerve-sheaths, the basocellular epithelial tumors, and the embryoma in the region of the testes and the ovary. It is not at all difficult to explain the presence of these tumors by displacement of cells in embryonic life, but the factor or factors which lead later in life to growth, either benign or malignant, in these congenital "Anlagen" we have not ascertained as yet.

From a large experience investigators are beginning to feel that a single or continuous trauma, or some form of irritation, may be a factor which leads to later growth.

The same is true of certain inflammatory tumors. As a rule, after a wound or an inflammation, the inflammatory reaction is sufficient to accomplish the healing of the wound, or the resolution of the inflammation, but in rare instances the inflammatory reaction is far out of proportion to the irritant. We observe this in certain keloid tumors, in the so-called desmoid tumors of the abdominal wall, in fibro-spindle-cell tumor formations, in areas of skin the seat of acne, in the so-called fibromatosis or linitis plastica of the wall of the stomach about an ulcer, in certain cases of chronic appendicitis, where the inflammatory thickening of the appendix is unusual, in some large inflammatory tumors of the colon about small diverticula. Nor can we explain why the new formation in the benign congenital tumor, or in the inflammatory tumor, remains benign in spite of the increased growth in some cases, while in others, at various intervals, malignant degeneration takes place.

In the treatment of such cases the possibility of a malignant change must always be borne in mind. It is on account of this possibility that surgeons now advocate the complete removal of all such benign congenital tumors and apparently benign inflammatory tumors.

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